

# Clinical Profile and Predictors of Mortality of Severe Pandemic (H1N1) 2009 Virus Infection Needing Intensive Care: A Multi-Centre Prospective Study from South India

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## ABSTRACT

**Background:** This multi-center study from India details the profile and outcomes of patients admitted to the intensive care unit (ICU) with pandemic Influenza A (H1N1) 2009 virus [P(H1N1)2009v] infection. **Materials and Methods:** Over 4 months, adult patients diagnosed to have P(H1N1)2009v infection by real-time RT-PCR of respiratory specimens and requiring ICU admission were followed up until death or hospital discharge. Sequential organ failure assessment (SOFA) scores were calculated daily. **Results:** Of the 1902 patients screened, 464 (24.4%) tested positive for P(H1N1)2009v; 106 (22.8%) patients aged 35±11.9 (mean±SD) years required ICU admission 5.8±2.7 days after onset of illness. Common symptoms were fever (96.2%), cough (88.7%), and breathlessness (85.9%). The admission APACHE-II and SOFA scores were 14.4±6.5 and 5.5±3.1, respectively. Ninety-six (90.6%) patients required ventilation for 10.1±7.5 days. Of these, 34/96 (35.4%) were non-invasively ventilated; 16/34 were weaned successfully whilst 18/34 required intubation. Sixteen patients (15.1%) needed dialysis. The duration of hospitalization was 14.0±8.0 days. Hospital mortality was 49%. Mortality in pregnant/puerperal women was 52.6% (10/19). Patients requiring invasive ventilation at admission had a higher mortality than those managed with non-invasive ventilation and those not requiring ventilation (44/62 vs. 8/44,  $P<0.001$ ). Need for dialysis was independently associated with mortality ( $P=0.019$ ). Although admission APACHE-II and SOFA scores were significantly ( $P<0.02$ ) higher in non-survivors compared with survivors on univariate analysis, individually, neither were predictive on multivariate analysis. **Conclusions:** In our setting, a high mortality was observed in patients admitted to ICU with severe P(H1N1)2009v infection. The need for invasive ventilation and dialysis were associated with a poor outcome.

**Key words:** Intensive care, SOFA, Swine flu, Ventilation

## INTRODUCTION

An outbreak of respiratory infection with a novel Influenza A virus occurred in early April, 2009. This Pandemic Influenza A(H1N1) 2009 virus [P(H1N1)2009v] demonstrated a high person-to-person transmission and was declared a pandemic by the WHO in June 2009.<sup>[1]</sup> The

first case of P(H1N1)2009v infection in India was reported in May 2009. Subsequently until December 2009, there were 26,039 confirmed cases in India with 967 deaths,<sup>[2]</sup> giving a case-fatality rate of 3.7%. Weekly trend analysis showed that case reporting in India peaked in August/September 2009 and reached a plateau or slightly declined thereafter.<sup>[1]</sup> The infection predominantly affected younger adults; 60% being 18 years or younger.<sup>[3]</sup> Pregnancy and metabolic conditions (including obesity) appeared to be associated with a higher risk for severe illness.<sup>[4]</sup>

A sub-group of patients who develop severe respiratory

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infection require intensive care unit (ICU) admission and prolonged organ support. Despite this being a small proportion, in the epidemic situation this has caused an enormous burden on ICU resources.<sup>[5]</sup> Whilst ICUs in developed nations have effectively handled this increased burden, in developing countries like India, the pandemic has placed severe limitations on the already restricted and stretched ICU resources. Compounding this issue in India was the initial reluctance to admit patients in non-governmental ICUs due to limitations in testing ability and drug availability (oseltamivir). Limited ICU beds in Government health institutions also resulted in sicker patients being referred, after initial evaluation and treatment, to the few ICUs that were admitting these patients. The Christian Medical College Hospital, St. John's Hospital, and Manipal Hospital were among the few hospitals in South India designated by the Government of India to diagnose and treat P(H1N1)2009v infection in the initial months of the pandemic. We detail the clinical profile and outcomes of patients admitted to the ICUs of these three hospitals during the initial four months of the P(H1N1)2009v epidemic.

## MATERIALS AND METHODS

Data from the ICUs of three hospitals in South India were collected prospectively from September 2009, when the first patient was admitted to these ICUs with P(H1N1)2009v infection. In November 2009, investigators from the three institutions agreed to pool their data. Admission source of patients included direct ICU admission via the emergency department (ED), transfer from other hospitals and patients from wards who had deteriorated after admission. In the initial phase of the epidemic, patients were screened for P(H1N1)2009v infection if they presented with an influenza-like illness or severe acute respiratory infection comprising fever, cough, dyspnea and presence of bilateral chest X-ray infiltrates, and any two of the following features-respiratory rate >30/minute, oxygen saturation (SpO<sub>2</sub>) <90% on room air, blood pressure <90 mm-Hg systolic, confusion or elevated blood urea nitrogen or creatinine. Within the first two weeks of the incident admission, we observed that patients with atypical radiological features (e.g., lobar consolidation) even in the absence of documented fever on hospitalization were tested positive for P(H1N1)2009v infection. These patients who were not screened at admission were subsequently tested as they had no clinical response. Thus, screening was subsequently expanded to include atypical presentations as outlined above. The diagnosis of P(H1N1)2009v infection was established by performing a real-time reverse transcriptase polymerase chain reaction (rRT-PCR)<sup>[6]</sup>

of respiratory samples (nasal-swab, throat-swab, or endotracheal aspirates) collected from these patients upon admission. Patients were treated with Oseltamivir orally or via a nasogastric tube. Initially the dose given was 75 mg twice daily for 5 days, which was increased after a month, due to a subsequent recommendation,<sup>[7]</sup> to a dose of 150-mg twice daily for 10 days, except when creatinine clearance was <10 ml/min/1.73m<sup>2</sup>, wherein a lower dose of 75-mg twice daily was administered. Patients were transferred to the ICU if they required mechanical ventilation or hemodynamic support. Supportive measures included mechanical ventilation, hemodynamic support, renal replacement therapy, and antibiotics when indicated. A trial of non-invasive ventilation (NIV) was considered based on guidelines for its use in acute respiratory failure. This included, severe dyspnoea at rest (RR >35/min), PaO<sub>2</sub>/FiO<sub>2</sub> ratio of <200 while breathing oxygen through a mask and use of accessory muscles of respiration or paradoxical abdominal motion.<sup>[8]</sup> Standard criteria were used to assess response to NIV or lack of it. This included clinical response (improvement in respiratory rate, Glasgow coma score (GCS)) and laboratory improvement (blood gases). Intubation was considered if there was (a) intolerance to the mask or contra-indication to continued use (e.g.) nasal bridge necrosis, (b) persistent hypoxemia not responding to appropriate and tolerated levels of Positive end expiratory pressure (PEEP) or (c) persistent or worsening respiratory acidosis. Other criteria for intubation included hemodynamic instability, reduction in GCS with inability to protect airway or clear secretions effectively or cardio-respiratory arrest. Skeletal muscle relaxants were considered in intubated patients with high respiratory support (Persistent hypoxemia despite FiO<sub>2</sub> >90% AND PEEP >12 cm H<sub>2</sub>O). An initial bolus of 8 mg of pancuronium was given intravenously, followed by an infusion at 4–8 mg/hr. Patients were followed up until death or discharge. Acute physiology and chronic health evaluation II (APACHE II) score at admission and daily Sequential organ failure assessment (SOFA) score<sup>[9]</sup> until death or discharge from ICU were calculated and recorded on all patients. All co-morbid illnesses, symptom profile and relevant biochemical, hematological and microbiological data, interventions and adverse events were recorded. Complications including nosocomial infections, pneumothorax, and pulmonary embolism were noted. Ventilator-associated pneumonia (VAP), catheter-related bloodstream infections (CRBSI) and catheter-related urinary tract infection (UTI) were diagnosed using standard case definitions.<sup>[10]</sup> Renal SOFA scores were used to monitor renal injury. Barotrauma was noted according to the criteria of Eisner *et al.*<sup>[11]</sup> The primary outcome of interest was hospital mortality. Other outcomes included need for and

duration of ventilation, tracheostomy and skeletal muscle relaxants, need for renal replacement therapy and duration of ICU and hospital stay. The study was approved by the institutional review boards of all three centres. Informed written consent was obtained from the patient's relative.

**Statistical aspects**

Statistical analysis was done using SPSS Version 16. Descriptive statistics were obtained for all study variables. All categorical variables were compared using Chi-square and Fisher's exact test and continuous variables using Student's *t*-test. All data were expressed as mean (±SD). Multivariate logistic regression analysis was also done to find the predictors of the outcome variable and expressed as odds ratio (OR) with 95% confidence limits (CI). For all the statistical analysis, *P*<0.05 was considered statistically significant. The graphs were generated using GraphPad Prism version 4.

**RESULTS**

**Baseline characteristics**

During the study period, 1902 adult patients were screened for P(H1N1)2009v infection; 464 (24.4%) were tested positive [Figure 1]. Of these, 106 patients (42 male; 64 female) aged 35.0±11.9 years, were admitted to the ICU 5.8±2.7 days after onset of illness. Admission sources were direct admission from the ED (*n*=62), transfer from medical wards (*n*=19) or from another hospital (*n*=25). Co-morbidities included respiratory disease (*n*=7), cardiovascular disease (*n*=5), morbid obesity (*n*=11), and diabetes (*n*=8); 9 patients were immunosuppressed by disease (collagen vascular disease, malignancy) or therapy (immunosuppressive drugs, steroids). Fourteen women presented during pregnancy and 5 in the post-partum period. Fever (96.2%), breathlessness (85.8%), and cough (88.7%) were the commonest symptoms [Table 1]. The admission APACHE II and SOFA scores were 14.4±6.5 and 5.5±3.1, respectively. Eighty-five patients (80.2%) fulfilled the criteria for acute respiratory distress syndrome (ARDS) at presentation to the ICU, while 11 (10.4%) had features consistent with a diagnosis of acute lung injury (ALI).

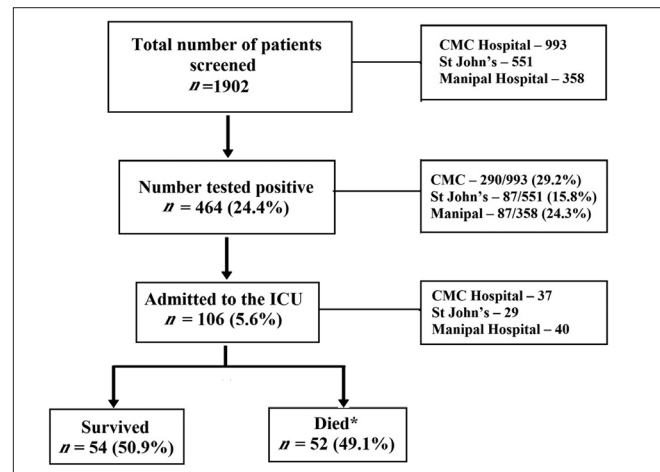
**Outcomes**

Mechanical ventilation was required in 96 (90.6%) patients; a trial of non-invasive ventilation (NIV) was given if clinically indicated (as outlined in methods). Of the 34 patients managed with NIV, 16 were weaned successfully while 18 patients who failed NIV were intubated and

invasively ventilated. The duration of NIV was 4.7±2.3 days in the 16 patients who required only NIV [Table 2]. Eighty (75.5%) patients required invasive mechanical ventilation for 10.7±7.9 days. Muscle relaxants were required in 62/80 (77.5%) patients for 7.6±5.9 days. Twelve (11.3%) patients underwent tracheostomy. Pneumothorax occurred in 9 patients.

Renal injury was observed in 43 patients (40.6%). Dialysis was required in 16 (15.1%) patients at 4.9±4.3 days following ICU admission; only 3 of these patients survived. Nosocomial infections, recorded from two centers (CMCH and Manipal) in 77 patients [Table 2] included VAP in 27 (35.1%), CRBSI in 8 (10.4%), and UTI in 5 (6.5%) patients. The organisms isolated from endotracheal aspirates included *Pseudomonas sp.* (*n*=8), *Acinetobacter baumannii* (*n*=6), *Escherichia coli* (*n*=2), *Klebsiella sp.* (*n*=2), *Staphylococcus aureus* (*n*=1), *Stenotrophomonas maltophilia* (*n*=1), and other non-fermenting Gram negative bacilli (*n*=8).

All 10 patients who did not require ventilatory support survived to hospital discharge. The duration of hospitalization for the entire cohort was 14.0±9.9 days.



**Figure 1:** Flow chart depicting the numbers screened, those positive and those requiring ICU admission. The number who died includes those who died and those who were discharged at request or against medical advice from hospital

**Table 1: Symptomatology of patients admitted with H1N1 infection**

Symptom	Number	Mean duration^ (days)	SD	CI
Fever	102	5.3	2.3	4.8 to 5.7
Cough	94	5.0	2.1	4.6 to 5.5
Breathlessness	91	2.3	1.3	2.1 to 2.6
Sore throat	11	4.4	2.8	2.5 to 6.3
Myalgia	07	4.7	2.1	2.8 to 6.6
Running nose	03	7.0	4.6	-4.4 to 18.4
Headache	02	2.5	2.1	-16.6 to 21.6

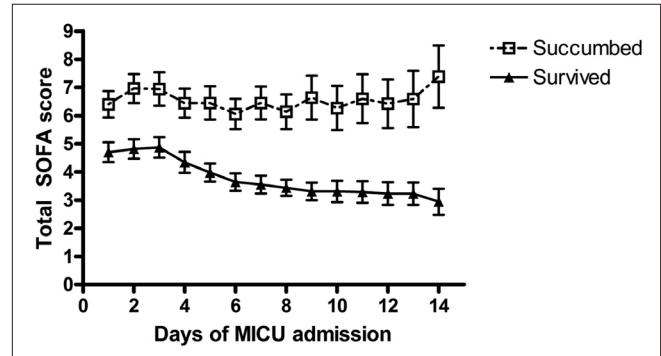
^Duration till ICU admission; SD: Standard deviation; CI: 95% Confidence interval

ICU and hospital mortality were 41 (38.7%) and 44 (41.5%), respectively. Eight patients (7.5%) were discharged upon request by the family, in view of very poor prognosis. The commonest causes of death were refractory hypoxemia and refractory septic shock with multi-organ dysfunction. Mortality in those managed only on NIV was 6.3% (1/16) and in those managed with NIV followed by invasive ventilation was 38.9% (7/18). Patients requiring invasive ventilation from admission had a mortality of 71% (44/62). The mortality in pregnant/post-partum women (10/19, 52.6%) was similar to non-pregnant patients (42/87, 48.3%).

**Predictors of mortality**

Non-survivors had significantly higher mean SOFA scores compared with survivors over the first 10-days of ICU admission [Figure 2]. Although the major contribution to the scores were respiratory and vascular scores [Figure 3], individually they did not demonstrate the same association as total scores. Univariate analysis [Table 3] showed an association between admission SOFA ( $P=0.004$ ) and APACHE-II ( $P=0.02$ ) scores and mortality. There was no gender predilection to mortality.

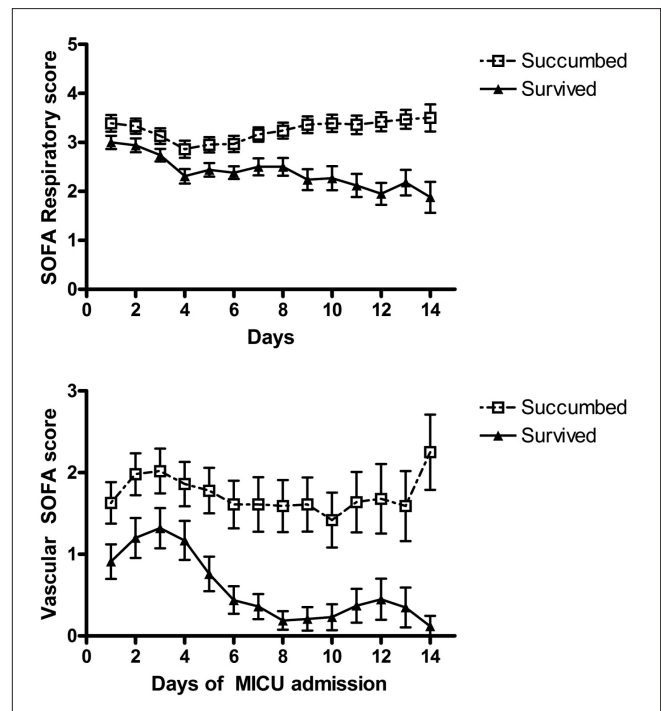
Patients who could be initiated and managed on NIV had a better survival ( $P<0.001$ ) compared with those who required invasive mechanical ventilation at the onset [Table 3]. However, the duration of ventilation was similar in survivors and non-survivors. The need for muscle relaxants was also significantly associated with mortality [Table 3]. The need for tracheostomy was not associated



**Figure 2:** Sequential total SOFA scores in ICU patients surviving from and succumbing to severe H1N1 infection. Daily sequential organ failure assessment (SOFA) scores on all patients admitted to the intensive care unit (ICU) with severe H1N1 infection, categorized as survivors and non-survivors. Scores are depicted as mean±standard error of mean (SEM). The mean scores were significantly ( $P<0.05$ ) different, on univariate analysis, between survivors and non-survivors from Day 1 through Day 14

Table 2: Outcome data		
Parameter	Value	95% CI
Mortality (Number, %)		
ICU mortality	41/106 (38.7)	0.29 to 0.49
Hospital mortality	44/106 (41.5)	0.32 to 0.51
Number discharged at request	08/106 (7.5%)	0.03 to 0.14
Ventilation (Number, %)		
Total number ventilated	96/106 (90.6)	0.83 to 0.95
Invasively ventilated	80/106 (75.5)	0.66 to 0.83
Non-invasively ventilated	34/106 (32.1)	0.23 to 0.42
Those NIV and invasive*	18/106 (17.0)	0.10 to 0.26
Only non-invasive ventilation	16/106 (15.1)	0.09 to 0.23
Duration of ventilation (days)		
All patients	10.0 (7.5)	8.60 to 11.64
Duration of non-invasive ventilation	3.1 (2.3)	2.25 to 3.87
Duration of invasive ventilation	10.7 (7.9)	8.92 to 12.44
NIV duration in those undergoing only NIV	4.7(2.3)	3.46 to 5.92
Other respiratory data		
Use of muscle relaxants (number, %)	62/106 (58.5)	0.49 to 0.68
Duration of use of muscle relaxants (days)	7.6 (5.9)	6.08 to 9.12
Number undergoing tracheostomy (%)	12/106 (11.3)	0.06 to 0.19
Renal replacement therapy		
Need for dialysis (number, %)	16/106 (15.1)	0.09 to 0.23
Day of initiation of dialysis	4.9 (4.3)	2.56 to 7.14
Duration of stay (days)		
Duration of stay in intensive care	10.8 (8.0)	9.23 to 12.29
Duration of stay in hospital	14.0 (9.9)	12.11 to 15.91
Infections (number developing, %)		
Ventilator associated pneumonia	27/77 (35.1)	0.25 to 0.47
Catheter related blood stream infections	08/77 (10.4)	0.05 to 0.19
Urinary tract infections	05/77 (6.5)	0.02 to 0.15

NIV: Non-invasive ventilation, Values in parentheses indicate standard deviation unless indicated; \*These patients initially were managed with NIV and if they failed, they underwent invasive ventilation



**Figure 3:** Sequential respiratory and cardiovascular SOFA scores of survivors and non-survivors. Respiratory (top panel) and cardiovascular (bottom panel) sequential organ failure assessment (SOFA) scores in patients admitted to the intensive care unit (ICU) with severe H1N1 infection, categorized as survivors and non-survivors. Scores are depicted as mean±standard error of mean (SEM)

**Table 3: Univariate analysis of factors that predict an unfavourable outcome in severe H1N1 infection**

Parameter	Survivors			Non-survivors <sup>A</sup>			P value
	N	Mean	SD	N	Mean	SD	
Age (years)	54	37.3	13.8	52	32.6	9.1	0.04*
Gender							
Male	20	-	-	22	-	-	0.81
Female	32	-	-	32	-	-	
Duration of fever (days)	53	5.4	2.1	49	5.2	2.5	0.64
Duration of cough (days)	47	5.4	2.4	47	4.6	1.7	0.06
Duration of breathlessness (days)	48	2.4	1.4	43	2.2	1.2	0.51
Admission APACHE II score	53	12.9	5.6	52	15.9	7.0	0.02*
Admission SOFA score	54	4.7	2.6	52	6.4	3.3	0.004*
Pregnancy status <sup>†</sup>							
Pregnant ~	9	-	-	10	-	-	0.73
Not pregnant	45	-	-	42	-	-	
Type of ventilation <sup>†</sup>							
Only NIV	15	-	-	1	-	-	<0.001*
Non-invasive and Invasive	11	-	-	7	-	-	
Only invasive	18	-	-	44	-	-	
Use of muscle relaxant							
Yes	19	-	-	43	-	-	<0.001*
No	35	-	-	9	-	-	
Need for tracheostomy							
Yes	8	-	-	4	-	-	0.247
No	46	-	-	48	-	-	
Ventilator associated pneumonia <sup>†</sup>							
Present	11	-	-	16	-	-	0.012*
Absent	35	-	-	15	-	-	
Serum creatinine <sup>†</sup>							
>1.4 mg/dl	15	-	-	28	-	-	0.01*
≤1.4 mg/dl	39	-	-	24	-	-	
Patients requiring dialysis <sup>†</sup>							
Needed dialysis	3	-	-	13	-	-	0.006*
Not required dialysis	51	-	-	39	-	-	
Duration of ventilation (days)	44	10.4	8.2	52	9.7	6.9	0.64
Duration of ICU stay (days)	54	11.2	8.8	52	10.4	7.1	0.60
Duration of hospitalization (days)	54	17.1	10.9	52	10.8	7.5	0.001*

<sup>A</sup> Includes those who died in hospital and those who were discharged at request or against medical advice; NIV: Non-invasive ventilation; N: Number of patients; SD: Standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential organ failure assessment; ICU: Intensive Care Unit; ~Includes immediate post-partum (n=5); \*Significant association (P<0.05); <sup>†</sup>Indicates number of patients for these parameters; Continuous variables analyzed by Student t-test whilst discrete variables analyzed by chi square test or Fisher's exact test

with an unfavourable outcome. Renal injury and need for dialysis were both associated with an increased risk (P=0.01 and P=0.006, respectively) of death [Table 3]. The development of VAP was associated (P=0.012) with mortality [Table 3], on univariate analysis. VAP was not incorporated in multivariate analysis as data was collected only from 2 centers.

Multivariate logistic regression analysis [Table 4] showed that mortality was associated with older age (OR 1.06, 95% CI 1.01 to 1.12), need for dialysis (OR 7.86, 95% CI 1.40 to 44.13) and need for invasive ventilation at admission (OR 10.63, 95% CI 3.68 to 30.70). Admission SOFA or APACHE II score were not independently associated with

**Table 4: Multivariate logistic regression analysis of factors associated with mortality in severe H1N1 infection**

Parameter	Odds ratio	Standard error	P value	95% CI
Age	1.060	0.026	0.027	1.007 to 1.117
Pregnancy	0.685	0.703	0.591	0.173 to 2.717
Duration of cough	1.032	0.100	0.755	0.847 to 1.256
Type of ventilation <sup>^</sup>	10.630	0.541	0.000	3.681 to 30.702
Need for dialysis	7.857	0.881	0.019	1.399 to 44.131
Admission SOFA score	0.852	0.091	0.852	0.713 to 1.017

<sup>^</sup> The type of ventilation was categorized as either 1–no ventilation, non-invasive ventilation alone or non invasive ventilation followed by invasive ventilation 2–invasive mechanical ventilation alone; SOFA: Sequential organ failure assessment

mortality on multivariate analysis.

## DISCUSSION

Influenza A viruses have caused seasonal epidemics and pandemics since the early 1900s. The P(H1N1)2009v, a newly emerged subtype of influenza A known popularly as “swine flu”, was the most common cause of influenza in humans in 2009. In India, the pandemic strain caused 967 deaths in 26,039 confirmed until December 2009, giving a case-fatality rate of 3.7%. Mortality was highest in the 20-39 age group (4.8%) and <5 age group (2.8%).<sup>[12]</sup> In a recent study from Pune, India, hospitalization and mortality rate from P(H1N1)2009v influenza was significantly higher than seasonal influenza A.<sup>[13]</sup>

The present study documents the characteristics of patients with P(H1N1)2009v infection admitted to ICUs in India. Whilst it is recognized that P(H1N1)2009v often causes a mild influenza-like illness in a majority of patients, a small proportion present with severe acute respiratory illness with organ dysfunction requiring ICU care. In the current study, of the 464 patients tested positive, 106 (22.8%) required ICU admission. In the cohort of patients admitted to hospitals in Mexico with P(H1N1)2009v infection, ICU admission was required only in 6.5%.<sup>[5]</sup> Our observations are consistent with a report from Australia of 112 hospitalized patients, where 30 (26.8%) required ICU admission.<sup>[14]</sup> Changes in the screening criteria in our institution, during the course of the pandemic, could have altered the proportion of patients tested positive.

Not surprisingly, the mortality of patients admitted to our ICUs in India was higher (41.5%) compared with cohorts from the developed world. In the earliest report of 18 patients in Mexico City admitted to an ICU with severe P(H1N1)2009v influenza infection, mortality was 58.3%.<sup>[15]</sup> However, the most recent reports from the US, Canada and Australia have reported much lower mortality rates of 11%

to 17.3%.<sup>[16-18]</sup> The reduced mortality over time in the larger cohorts probably reflects a better understanding of the disease process as well as early identification and treatment of the illness. Although not determined in our study, we observed that survival tended to be better over time with our increased understanding of the disease. Several factors may have contributed to a high mortality in our patients compared with cohorts from developed countries. These may include differences in patient characteristics, delayed presentation, limitation of treatment due to lack of resources (financial and technological), higher incidence of nosocomial infections and complications and lack of preparedness to deal with pandemics. Poverty and poor access to medical care have been shown to impact mortality from this infection even in developed countries with populations such as native Americans and Alaskans, having a four-times higher mortality compared with persons of all other racial/ethnic populations combined.<sup>[19]</sup> A similar observation from Australia also suggests a higher hospitalization rate due to influenza in the indigenous population.<sup>[20]</sup> A recent report on patients admitted to ICU in a developing country (Argentina) for severe H1N1 illness reported a similar mortality to ours of 46%.<sup>[21]</sup>

An association between admission SOFA score and mortality was explored. This initially appeared to be significant on univariate analysis. We also observed that SOFA scores appeared to increase in the first 5-days following ICU admission in non-survivors and decreased in the first 4-days in survivors. This therefore may be a useful tool to assist the physician in family counseling as well as prognostication during the course of illness, particularly when resource constraints may restrict the continued provision of ICU care in those who require prolonged ventilation. SOFA score, although predicting outcome on univariate analysis, failed to predict outcome when adjusted for other variables [Table 4]. APACHE-II scores have been shown to be a predictor of mortality in some cohorts of severe P(H1N1)2009v infection.<sup>[21,22]</sup> Our study whilst demonstrating an association on univariate analysis, again failed to show an association on multivariate analysis.

Oseltamivir was administered as the anti-viral agent for all of our patients. The first 8 patients were treated with 75-mg twice daily of oseltamivir for 5 days. With the subsequent recommendation to increase the dose, this was modified to 150-mg twice daily for 10 days. The higher dose was used in view of the poor gastrointestinal absorption in critically ill patients, whilst the increase in duration was implemented because of the prolonged viral shedding in critically ill patients.<sup>[7]</sup> An additional 31 patients received a lower dose (75mg BD) of oseltamivir for a period of

10 days, in view of a reduced creatinine clearance ( $<10$  ml/min/1.73m<sup>2</sup>). Parenteral neuraminidase inhibitors (peramivir or zanamivir) were not available in our country. In one centre where a repeat PCR was performed on a limited number of patients ( $n=11$ ) on Day 5, six patients continued to be positive whilst 5 patients cleared the virus. Of the 6 patients who did not clear the virus on Day 5, five showed at least  $1 \log_{10}$  (range  $\log_{10}$  0.8–3.2) fall in virus titer whilst one patient showed a  $1.1 \log_{10}$  increase in titer. A third sample was not available for this patient. Of the 5 patients that cleared the virus the fall in titer was at least  $1.6 \log_{10}$  (range 1.6–5.3).

There were initial concerns regarding the use of NIV in the management of severe P(H1N1)2009v infection in view of the risk to health personnel. Expert recommendations were that invasive mechanical ventilation, with a lung-protective strategy, should be the initial approach for managing patients with P(H1N1)2009v infection complicated by acute respiratory distress syndrome.<sup>[23]</sup> Several reasons compelled the use of NIV in our setting and included: (1) The large amount of experience that our medical and nursing personnel have had with the use of NIV; (2) the fact that self-ventilated patients with proven H1N1 infection who are admitted to the Isolation ward pose probably the same risk to our staff as those who are admitted in an isolation area in the ICU with staff using similar (if not more) personal protection methods; (3) the impression that NIV is associated with lower infection and complication rates when compared with invasive ventilation (in other clinical settings) and that a “trial” of NIV was “worthwhile”; (4) resource and cost constraints that influenced our decision to “try” NIV (if patient fulfilled the criteria). Along with this decision, prospective surveillance (healthcare workers developing ILI had to be screened promptly) and a seroprevalence study (at the end of 4 months) were done in one centre to assess if healthcare workers in the ICU were at added risk of infection in view of these policies. The study showed that when personal protection devices were used, healthcare workers in the ICU were not at an increased risk of acquiring P(H1N1)2009v infection when compared with healthcare workers working in other areas.<sup>[24]</sup>

Thus, 34 of the 96 patients were managed initially with NIV; 16 patients (47.1%) were weaned successfully without the need for invasive mechanical ventilation. The significantly lower mortality in patients managed with NIV whilst suggesting effectiveness of NIV, may be a surrogate marker of severity of illness, with less sick patients successfully managed with NIV and the more severely ill patients failing NIV and needing to be intubated and ventilated. The significant association between invasive ventilation

and mortality, despite adjusting for severity of illness and other parameters [Table 4] is interesting. However, as only a small number were treated with NIV, caution should be exercised in attributing a positive association between NIV and good outcome. Unlike the rapid response to NIV in diseases such as cardiogenic pulmonary edema and chronic obstructive pulmonary disease, patients with respiratory failure secondary to severe P(H1N1)2009v infection needed NIV for  $4.7 \pm 2.3$  days with 4 patients requiring it for over 7 days.

Pregnancy has been identified as a risk factor for severe illness. In the present study, of admissions to ICU for P(H1N1)2009v, mortality rates did not significantly differ between pregnant/post-partum (10/19, 52.6%) women and non-pregnant (48.3%) patients. In several North American series, mortality among pregnant women with P(H1N1)2009v infection admitted to ICU was 11–25%.<sup>[25-27]</sup>

VAP was noted in 35.1% of our patients and was much lower than the 52.6% from a recent series in South Africa.<sup>[22]</sup> Although VAP was associated with a higher mortality ( $P=0.012$ ) on univariate analysis in our cohort, this association could not be tested on the multivariate analysis. Renal injury was noted in 43/106 (40.6%) patients of whom 16 (15.1%) required dialysis. The need for dialysis was associated with increased odds of death on multivariate analysis. In a recent report of 22 patients with P(H1N1)2009v from Argentina, 14 (63.6%) developed acute kidney injury. Three of the four patients who required dialysis died.<sup>[28]</sup> In another cohort of 13 patients from Australia, 8 (61.5%) were diagnosed to have acute kidney injury with 3 (23.1%) developing failure and requiring renal replacement therapy.<sup>[29]</sup>

## CONCLUSION

Severe P(H1N1)2009v infection requiring ICU admission, in our cohort, was associated with significant morbidity and mortality. The need for invasive ventilation and dialysis were associated with a poor outcome. Whilst scoring systems such as the SOFA and APACHE II did not reliably predict outcome in our cohort, serial SOFA scores may help prognostication during the course of ICU admission.

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