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# Clinical Profile and Predictors of Mortality in H1N1 and Non-H1N1 Related ARDS in a Tertiary Care Center in South India

Research Article

Mahendra M[1], Jayaraj BS[2], Chaya SK[3], Mahesh PA[4*]

[1] Assistant Professor in Pulmonary Medicine, Shimoga Institute of Medical Sciences, Shivamogga, Karnataka, India.
[2] Professor of Pulmonary Medicine, JSS Medical College, JSS University, Mysore, India.
[3] Assistant Professor in Pulmonary Medicine, JSS Medical College, JSS University, Mysore, India.
[4] Professor and Head of Pulmonary Medicine, JSS Medical College, JSS University, Mysore, India.

## Abstract

**Introduction:** H1N1 influenza has caused significant mortality across the world mostly due to ARDS. It is important to differentiate H1N1 ARDS from non-H1N1 ARDS for early treatment and also to study predictors of mortality in ARDS patients.
**Methodology:** Prospective study was done in patients with ARDS admitted to RICU. Clinical characteristics and outcomes were compared among H1N1 and non-H1N1 ARDS. Cox regression was done for survival analysis.
**Results:** 97 patients were admitted with ARDS. 59 were positive for H1N1. H1N1 ARDS patients had higher APACHE2 score, shorter duration of symptoms, worse hypoxemia compared to non-H1N1 ARDS. There was no difference in mortality between H1N1 and non-H1N1 ARDS. On multivariate Cox regression analysis, higher APACHE2 score, need for invasive ventilation and prolonged ICU were associated with increased mortality.
**Conclusion:** Acute respiratory symptoms with severe hypoxemia, lymphopenia can be helpful to suspect H1N1 influenza in periphery for early referral. On multivariate Cox regression, higher APACHE2 score, prolonged ICU and need for invasive ventilation were independently associated with higher mortality.

**Keywords:** H1N1; Non-H1N1; ARDS; Mortality; ICU.

**Abbreviations:** OGTT: Oral Glucose Tolerance Test; APACHE II: Acute Physiology and Chronic Health Evaluation II; CDC: Centers for Disease Control and Prevention; BAL: Bronchoalveolar Lavage; NIV: Noninvasive ventilation; FIO2: Fraction of Inspired Oxygen; ADA: American Diabetes Association; FPG: Fasting Plasma Glucose.

## Introduction

H1N1 influenza pandemics have caused significant mortality and healthcare burden across the world mostly due to lower respiratory tract infections. In the recent pandemic caused by novel H1N1 influenza virus in 2009 resulted in 277,607 cases and 3205 deaths [1]. Although there were few sporadic cases in post pandemic phase, WHO had warned of possible localized outbreaks especially in India and New zealand [2]. In 2014, there was resurgence of H1N1 epidemic in India causing 33000 cases that claimed 2000 lives [3]. H1N1 influenza presents with a broad spectrum of clinical manifestations ranging from mild flu to fulminant pneumonia and acute respiratory distress syndrome (ARDS). Patients with H1N1 pneumonia often exhibit rapidly progressive refractory hypoxemia requiring invasive ventilation in around 80% of patients admitted to ICU [4].

Incidence of ARDS was found to be 6.6-19.7 per 100000 person-years in various studies done across world [5-8]. Worldwide, severe sepsis is most common trigger for ARDS. Other triggers include Pneumonia, polytrauma, severe burns, massive blood transfusion and Pancreatitis. Etiology of ARDS in India differs from western countries with higher incidence of ARDS due to tropical diseases like malaria, dengue, leptospirosis next to Pneumonia [9]. In developed countries mortality rates in these ARDS patients have been showing a declining trend which was 70% in 1990 to 51% in

***Corresponding Author**:
Dr. Mahesh PA, DNB (TB and respiratory disease),
Professor and Head of Pulmonary Medicine, JSS Medical College, JSS University, Mysore, India.
Tel: 9448044003
E-mail: mahesh1971in@yahoo.com

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1999 to 26% in 2005 mainly due to better management of ventilation strategies [10-12]. In India mortality rates are comparatively higher and vary between 44-57% [9-13].

It is observed that H1N1 pneumonia causes more severe disease with higher mortality compared to other community acquired pneumonia [14]. It is noteworthy that H1N1 affects relatively younger healthy population [15]. It is very important to differentiate clinically between H1N1 and Non-H1N1 ARDS patients during flu outbreak in order to identify, triage and treat H1N1 pneumonia early with antiviral agents and also it is important to study predictors of mortality among patients with ARDS as there is scarce data in Indian population.

## Methodology

### Study Design

We conducted a prospective observational study of all patients presenting with acute onset of fever, cough and dyspnea with bilateral opacities on chest x-ray admitted to Respiratory ICU in a tertiary care teaching hospital during the period December- June 2016. All patients were subjected to throat swab for H1N1. Patients getting admitted to ICU with ARDS were included into study after obtaining informed consent. Clinical characteristics, Course of illness, radiological and laboratory investigations and survival were compared among patients with H1N1 and non H1N1 ARDS patients. Patients who succumbed within 1 hour of admission and patients refusing to consent were excluded from the study.

### Data Collection

We collected information on patient demographics, clinical symptoms and duration, comorbid conditions like diabetes, hypertension, COPD and IHD, risk factors such as smoking and alcohol consumption were recorded. Clinical parameters such as pulse rate, respiratory rate, blood pressure and oxygen saturation and laboratory parameters such as chest x-ray, complete hemogram, serum electrolytes, liver function test, renal function tests and arterial blood gas analysis were recorded. Severity of illness was assessed using Acute Physiology and Chronic Health Evaluation II (APACHE II) at admission.

Description of procedures and investigations undertaken: Throat swab for H1N1 was taken on the day of admission. Single sample of nasopharyngeal swab was taken under strict aseptic precautions from the posterior pharyngeal wall and bronchial-aspirate samples were obtained from patients on ventilator and put in a sterile container containing 3ml of viral transport media - HiViral (Himedia) and sent in cold chain, to Kasturba Medical College (KMC), Manipal, which is a government approved lab for detecting H1N1. Samples reached the lab within 24-48 hours. The samples were analyzed by Taqman Real-Time PCR for influenza-A, influenza-B, swine flu-A, swineflu-H1 in accordance with published guidelines from the U.S. Centers for Disease Control and Prevention (CDC). Results were obtained on 5$^{th}$ day from the day of sample dispatch.

### Sputum Collection

A single sputum sample in a sterile wide mouthed container was obtained within 24 hours of admission to ICU, early morning sample whenever possible. At least 15 ml of sputum was collected and sample was considered adequate if the sample was mucopurulent on gross visual examination. Sample was sent to lab immediately. Specimen was considered satisfactory if the sample had than 10 squamous epithelial cells and ≥25 leukocytes per high power field, as well as presence of alveolar macrophages. Blood agar and MacConkey agar was used for quantitative cultures and >$10^6$ CFU/ml on quantitative culture was considered pathological.

### Induced Sputum

In patients who were conscious and unable to expectorate satisfactory sputum sample, induction of sputum was done using 20 ml of 3% saline nebulization in a well ventilated room for 5 minutes. Patient was asked to attempt forceful cough and sputum yield of 2ml was considered satisfactory. Procedure was terminated if patient complained of dyspnea, chest pain and wheeze. Patients with hemodynamic instability, asthma, hypoxemia (SPO2 <88% at room air) were excluded from this procedure [16].

### Bronchoalveolar Lavage (BAL)

BAL was done in selected patients to rule out malignancy and in whom microbiologic diagnosis was not established. Bronchoalveolar lavage was performed as per ATS guidelines [17]. BAL was taken using a portable flexible bronchoscopy Olympus, 2.6mm diameter, around 100-120 ml of normal saline was instilled through bronchoscope and instilled saline was retrieved using negative suction pressure of 50-80 mm Hg adjusted to avoid visible airway collapse. Sample was considered adequate if the minimal total volume retrieved was more than or equal to 5% of the instilled volume. BAL samples were processed similar to sputum samples. BAL samples were considered satisfactory if there were ciliated cells, alveolar macrophages and <5% squamous epithelial cells. BAL quantitative culture >$10^4$ CFU/ml was considered pathological.

### Blood Culture

Blood culture was done in patients with suspected bacteremia and sepsis. Skin was cleaned with 70% isopropyl alcohol and two sets of blood cultures of 10 ml each were taken from each arm.

Patients requiring mechanical ventilation, requiring a fraction of inspired oxygen (FiO2) greater than or equal to 60%, receiving intravenous infusion of inotropes or vasopressors were admitted to ICU. A trial of non-invasive ventilation (NIV) was considered as per the recent guidelines for acute respiratory failure [18]. Severity of ARDS was assessed by PaO2/FiO2 ratio (200-300- mild, 100-200- moderate and <100 severe). Patients with ARDS were managed as per ARDS net protocol with low tidal volume and high PEEP [19].

Non invasive ventilation was tried in all patients with PaO2/FiO2 >150 mm Hg. Face mask (Philips respironics) was used to deliver NIV via ventilator in all patients. Size of face mask was selected based on measurement from eyebrows to bottom of the chin to ensure a tight but comfortable seal. NIV titrations of pressures were set according to standard protocol: inspiratory pressure was increased in increments of 2-3 cm $H_2O$ to achieve respiratory rate <25/min and disappearance of usage of accessory muscle

of respiration. PEEP was increased in 2-3 cm $H_2O$ increments and aimed to achieve saturation >90% with FiO2 <60%. Patients with impending cardiorespiratory failure, Glascow coma score <8, Vomiting, tracheostomy, increased intracranial pressure and uncooperative patients were excluded from NIV trial. Vitals were closely monitored and if there was no improvements in vitals and if clinical symptoms worsen in half an hour of NIV trial, patients were switched to invasive ventilation.

Arterial Blood gas analysis was done in ABL FLEX 800 machine (Radiometer), Serum electrolytes in DIESTRO electrolyte analyzer, liver and renal function tests in TOSHIBA TBA 120 FR a fully automated chemistry analyzer. Complete hemogram was analyzed in NIHON KOHDEN (5 part differential cell counter) and SYSMEX (6 part differential cell counter). Hemoglobin was quantified by Cyanmeth hemoglobin method and platelet count and total count was quantified using Flow-cytometer.

We defined ARDS and severity of ARDS as per Berlin definition," the acute onset of respiratory failure, bilateral infiltrates on chest radiograph, hypoxemia as defined by a PaO2/FiO2 ratio ≤300 mmHg, and no evidence of left atrial hypertension or a pulmonary capillary pressure <18 mmHg (if measured) to rule out cardiogenic edema" [20].

We defined lymphopenia as lymphocytes ≤ 20% of total leukocytes [21] and Leukopenia as WBC count <4.5X $10^9$/ml [22].

We defined smoking as " An adult who has smoked 100 cigarettes in life time and who currently smokes cigarettes" [23].

We defined Alcoholism as chronic alcohol use to the degree that interferes with physical and mental health, or with normal social or work behavior [24].

We defined Diabetes mellitus as per American Diabetes Association (ADA) as, A hemoglobin A1c (HbA1c) level of 6.5% or higher or A fasting plasma glucose (FPG) level of 126 mg/dL (7 mmol/L) or higher; fasting is defined as no caloric intake for at least 8 hours, or A 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), or A random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia (ie, polyuria, polydipsia, polyphagia, weight loss) or hyperglycemic crisis [25].

We defined Hypertension as per blood pressure >130 mm Hg systolic and >80mm Hg diastolic pressure.

### Ethics

The Institutional Ethics Committee approved the study IEC no-JSS/MC/IEC/05/5237/2015-16. Informed consent from patient/legal representative was taken prior to inclusion in the study.

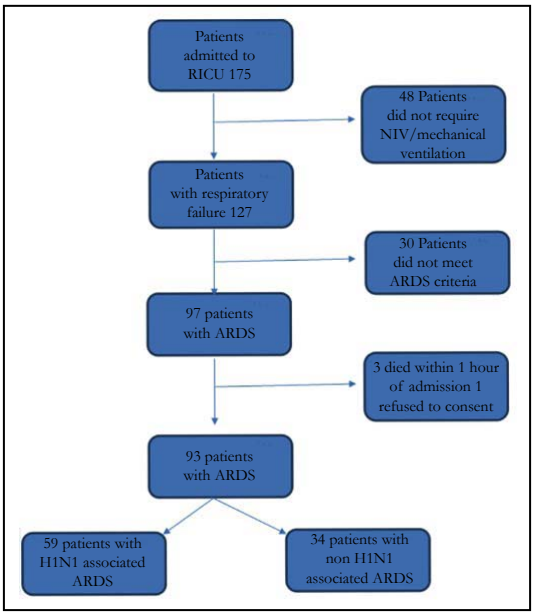
### Statistical Methods

Descriptive data are presented as frequencies (percentages) for discrete variables and as means (SDs) for continuous variables. For comparisons between two groups, Mann-Whitney U test was used or, when appropriate, the two-sample t-test. Chi-square test was used to evaluate categorical factors. Kaplan meier analysis and Cox regression analysis was done for survival in patients with ARDS. All statistical tests were 2-tailed, and factors were considered statistically significant at p <0.05. IBM SPSS version 22 and CDC Epi Info version 7 was used for analysis.

## Results

In our prospective study, we found 97 patients (55.4% of total) were admitted to respiratory ICU with diagnosis of ARDS (Figure 1). Four patients were excluded from the study (three patients succumbed within 1 hour of admission and 1 patient refused to consent). Fifty nine patients tested positive for H1N1 and 34 patients tested negative for H1N1. Patients with H1N1 ARDS had higher proportion of Cough (100%), Dyspnea (94.92%) and sore throat (42.37%) at presentation compared to non H1N1 ARDS patients. Co-morbidities were noted in 42(45%) of patients and diabetes mellitus (27.96%) was the most common comorbid-

**Figure 1. Flowchart depicting enrollment of cohort.**



ity. All patients were started on oseltamivir 75mg BD based on clinical symptoms as per guidelines given by WHO [26] and was stopped if throat swab for H1N1 was negative.

Forty four percent (26/59) of patients with H1N1 associated ARDS needed invasive ventilation and Forty seven percent (28/59) of patients needed NIV. Twenty six percent (9/34) of patients needed invasive ventilation and Seventeen percent (6/34) of patients were put on NIV among patients with non H1N1 ARDS. We identified organisms other than H1N1 in 28% (26/93) of the patients. Isolation rate of organisms varied biological specimens: Blood culture (4/14, 28.5%), Endotracheal aspirate (12/35, 34.3%), Sputum culture (3/13, 23%) BAL (6/8, 75%), Urine culture (1/3,33%).Ventilator associated pneumonia was seen in 12 patients (36.36%). Acinetobacter baumanii was the most common organism isolated (9/26, 34.6%) followed by Streptococcus (6/26, 23%), Klebsiella pneumoniae (5/26, 19.2%). We did not observe barotrauma in patients on ventilator. Mortality rate among patients with H1N1 associated and non H1N1 associated ARDS was 40.67% and 26.47% respectively (Figure 2).

We found H1N1 associated ARDS patients had higher APACHE2 score and worse hypoxemia at admission compared to non H1N1 ARDS (Table 1). Duration of hospitalization was more in patients with H1N1 associated ARDS (7.72 vs 6.11 days). There was significantly lower leukocyte count in H1N1 associated ARDS patients (8.37 vs 15.05 $X10^3/mm^3$).We found lower lymphocyte count in patients with H1N1 associated ARDS (34 % vs 59%). However we did not find any statistical difference in mortality rates among patients with and without H1N1 associated ARDS.

We found on univariate Cox regression analysis, patients with ARDS with higher APACHE2 score, presence of diabetes, smoking, prolonged ICU stay, use of invasive ventilation, prolonged duration of invasive ventilation, requiring vasopressors, longer duration of symptoms, low platelets were associated with increased risk for mortality (Table 2). On multivariate Cox regression analysis, we found patients with higher APACHE2 score, need for invasive ventilation and prolonged ICU stay were associated increased hazard for mortality (Table 3).

## Discussion

The epidemic of H1N1 in 2015 claimed many lives in India mostly young and previously healthy. The global H1N1 2009 pandemic has been studied well, but the epidemic that occurred in India has sparse data. H1N1 patients have more severe ARDS than non H1N1 ARDS patients requiring advanced rescue strategies [27, 28]. In the present study we observed that patients with H1N1 associated ARDS had shorter duration of symptoms, higher incidence of sorethroat, higher APACHE2 score at admission, need for invasive ventilation, vasopressor usage, relative lymphopenia, lower leukocyte count compared to non H1N1 ARDS patients. Although nearly 46% of patients with H1N1 ARDS required invasive ventilation, there was no difference in mortality rates among H1N1 and non H1N1 ARDS patients. On Multivariate cox regression analysis for mortality predictors among ARDS patients, we found higher APACHE2 score, need for mechanical ventilation and shorter duration of ICU stay were independently associated with increased hazard for mortality.

Factors that are more commonly observed in H1N1 ARDS patients than in non-H1N1 pneumonia patients include younger age, female gender, leucopenia, obesity, lesser comorbidties, lower C-reactive protein, higher lactate dehydrogenase, lower PaO2/FiO2 ratio, bilateral radiological opacities [29-35]. A 5 point regression model was developed by Bewick et al., to identify clinical variables most predictive of H1N1 pneumonia which included age <65, WBC <12000/$mm^3$, bilateral radiological opacities, oriented mental status, temperature >38°C [34]. We did not find any statistical difference in age and temperature between the cohort however we did find lower WBC counts and bilateral radiological opacities in patients with H1N1 ARDS patients which was statis-

**Figure 2. Kaplan Meier plot depicting differences in survival among patients with H1N1 and Non H1N1 ARDS.**

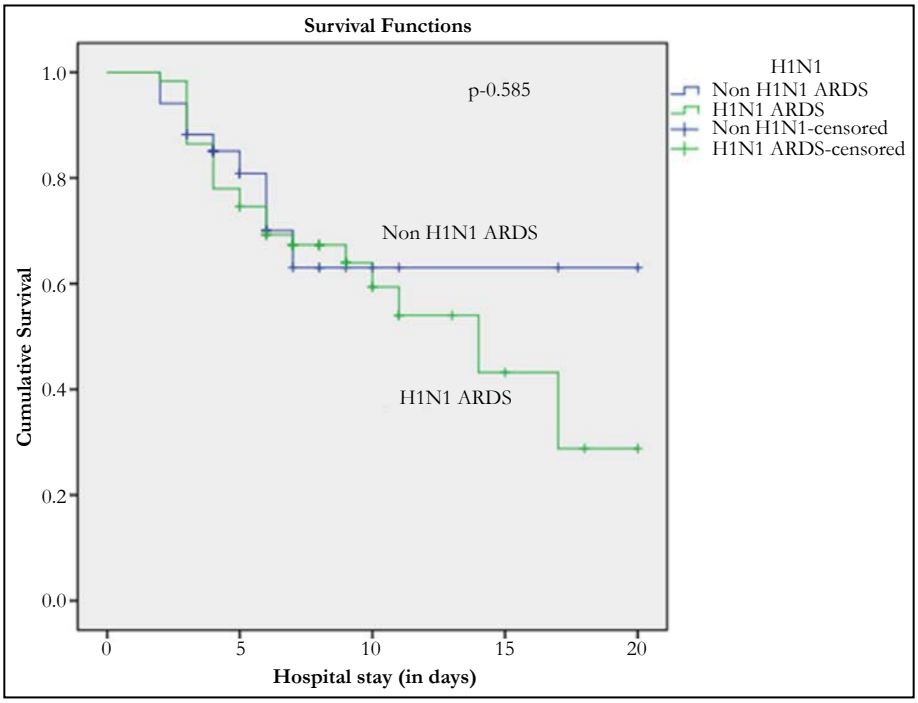


**Table 1. Baseline Characteristics of patients with H1N1 ARDS and Non H1N1 ARDS.**

| Variables | Total (93) | H1N1 ARDS (59) | Non H1N1 ARDS (34) | P value |
|---|---|---|---|---|
| Age in years, mean (SD) | 43.21 (13.82) | 43.25 (12.35) | 43.14 (16.27) | 0.791 |
| Gender, Male, n (%) | 40 (43.01) | 22 (37.29) | 18 (52.94) | 0.210 |
| Comorbidities, n (%) | | | | |
| Diabetes | 26 (27.96) | 15 (25.42) | 11 (32.35) | 0.63 |
| COPD | 7 (7.53) | 4 (6.78) | 3 (8.82) | 0.703 |
| Asthma | 12 (12.90) | 6 (10.17) | 6 (17.65) | 0.34 |
| Hypertension | 11 (11.83) | 8 (13.56) | 3 (8.82) | 0.740 |
| Smoking, n(%) | 20 (21.51) | 13 (22.03) | 7 (20.59) | 0.921 |
| Alcoholism, n (%) | 6 (6.45) | 4 (6.78) | 2 (5.88) | 0.788 |
| Duration of symptoms in days, mean (SD) | 6.30 (4.14) | 5.42 (2.58) | 7.82 (5.69) | 0.0065 |
| Non Invasive Ventilation, n (%) | 38 (40.86) | 35 (59.32) | 3 (8.82) | 0.0000053 |
| Invasive ventilation, n(%) | 35 (37.63) | 26 (44%) | 9 (26) | 0.00000001 |
| Duration of invasive ventilation, mean (SD) | 3.67 (2.78) | 4.12 (2.43) | 2.14 (1.46) | 0.469 |
| Vasopressor usage, n (%) | 16 (17.20) | 14 (23.73) | 2 (5.88) | 0.04 |
| APACHE2 Score at admission, mean (SD) | 9.54 (4.74) | 10.25 (3.12) | 8.38 (2.45) | 0.015 |
| PaO2/FiO2, mm Hg, mean (SD) | 196 (75.49) | 170 (74.43) | 240.94 (53.66) | 0.00001 |
| PCO2 mm Hg, mean(SD) | 33.22 (10.57) | 32.62 (6.94) | 34.05 (14.23) | 0.49 |
| Leukocyte count, $X10^3/mm^3$, mean (SD) | 10.81 (8.73) | 8.37 (6.98) | 15.05 (9.87) | 0.00026 |
| Neutrophil count,%, mean (SD) | 79.54 (9.58) | 79.91 (7.12) | 78.83 (13.17) | 0.395 |
| Lymphocyte count,%, mean (SD) | 21.85 (17.38) | 17.22 (10.13) | 30.63 (24.01) | 0.018 |
| Platelet count, X $10^6/mm^3$, mean (SD) | 1.80 (0.89) | 1.77 (0.75) | 1.85 (1.10) | 0.665 |
| Length of ICU stay, mean (SD) | 5.27 (2.82) | 5.78 (2.99) | 4.38 (2.27) | 0.339 |
| Length of hospital stay, mean (SD) | 7.13 (3.89) | 7.72 (3.83) | 6.11 (3.83) | 0.011 |
| Mortality, n(%) | 33 (35.48) | 24 (40.68) | 9 (26.47) | 0.248 |

**Table 2. Univariate Cox Regression Analysis for Factors Associated with Mortality in Patients with ARDS.**

| Variables | Total (93) | HR (95% CI) | P value |
|---|---|---|---|
| Age in years, mean (SD) | 43.21(13.82) | 1.01(0.99-1.04) | 0.172 |
| Gender, Male, n (%) | 40(43.01) | 1.43(0.71-2.85) | 0.307 |
| Comorbidities, n (%) | | | |
| Diabetes | 26(27.96) | 2.34(1.16-4.71) | 0.017 |
| COPD | 7(7.53) | 1.93(0.67-5.54) | 0.221 |
| Asthma | 12(12.90) | | |
| Hypertension | 11(11.83) | 1.81(0.74-4.41) | 0.19 |
| H1N1 infection, n (%) | 59(63.4) | 1.23(0.57-2.66) | 0.596 |
| Smoking, n (%) | 20(21.51) | 2.12(1.01-4.45) | 0.044 |
| Alcoholism, n (%) | 6(6.45) | 2.57(0.89-7.42) | 0.080 |
| Duration of symptoms in days, mean (SD) | 6.30(4.14) | 1.12(1.03-1.21) | 0.005 |
| Non Invasive Ventilation, n (%) | 38(40.86) | 0.83(0.41-1.68) | 0.262 |
| Invasive ventilation, n(%) | 35(37.63) | 14.54(5.09-41.53) | 0.000 |
| Duration of invasive Ventilation, mean(SD) | 3.67(2.78) | 1.12(1.03-1.22) | 0.006 |
| Vasopressor usage, n (%) | 16(17.20) | 3.82(1.89-7.73) | 0.0001 |
| APACHE2 Score at admission, mean (SD) | 9.54(4.74) | 1.13(1.06-1.21) | 0.000 |
| PCO2 mm Hg, mean(SD) | 33.22(10.57) | 1.01(0.98-1.04) | 0.355 |
| Leukocyte count, $X10^3/mm^3$, mean(SD) | 10.81(8.73) | 0.96(0.91-1.02) | 0.235 |
| Neutrophil count,%, mean(SD) | 79.54(9.58) | 1.02(0.98-1.07) | 0.208 |
| Lymphocyte count,%, mean(SD) | 21.85(17.38) | 0.98(0.95-1.01) | 0.313 |
| Platelet count, at admission X $10^6/mm^3$,mean(SD) | 1.80(0.89) | 0.59(0.39-0.90) | 0.014 |
| Length of ICU stay, mean (SD) | 5.27(2.82) | 0.76(0.62-0.93) | 0.01 |

**Table 3. Multivariate cox regression analysis for factors associated with mortality in patients with ARDS.**

| Variables | HR (95% CI) | p value | Adj HR(95% CI) | p value |
|---|---|---|---|---|
| *APACHE2 score at admission | 1.13 (1.06-1.21) | 0.0001 | 1.12 (1.02-1.20) | 0.016 |
| Diabetes Mellitus | 2.34 (1.16-4.71) | 0.017 | 0.96 (0.42-2.15) | 0.925 |
| Smoking | 2.12 (1.01-4.45) | 0.044 | 1.32 (0.57-3.02) | 0.510 |
| Duration of symptoms | 1.12 (1.03-1.21) | 0.005 | 1.06 (0.97-1.16) | 0.140 |
| Duration of ICU stay | 0.76 (0.62-0.93) | 0.010 | 0.59 (0.45-0.77) | 0.0001 |
| Invasive ventilation | 14.54 (5.09-41.53) | 0.0001 | 18.83 (4.51-78.58) | 0.0001 |
| Duration of invasive ventilation | 1.12 (1.03-1.22) | 0.006 | 1.07 (0.83-1.39) | 0.566 |
| Vasopressor usage | 3.82 (1.89-7.73) | 0.0001 | 1.77 (0.74-4.19) | 0.194 |
| Low Platelet count at admission | 0.59 (0.39-0.90) | 0.014 | 0.84 (0.50-1.41) | 0.518 |

tically significant.

There are several noteworthy observations in patients with H1N1 ARDS compared to non-H1N1 ARDS. First, we found H1N1 associated ARDS patients had higher severity of illness as identified by APACHE2 score than non H1N1 ARDS at admission. Higher APACHE 2 score was largely driven by severe hypoxemia and we noted less extra pulmonary organ failure in H1N1 ARDS patients. Development of severe ARDS in H1N1 influenza pneumonia may be due to induction of aberrant immune response to virulent viral infection, causing extensive lung damage [36]. It also been observed that patients with H1N1 pneumonia are more predisposed to pulmonary embolism there by accounting for refractory hypoxemia, although there is no sufficient data to substantiate it [37]. A retrospective study done in Delhi in 2009-10 found patients with H1N1 ARDS had severe hypoxemia similar to our study [38]. Similarly an US study in 2009 also found severe hypoxemia as a major factor in higher severity of illness score in H1N1 associated ARDS patients [27]. An Indian study done in 2009 also found severe hypoxemia to be predominant feature in all patients with H1N1 patients [39].

Second, we found patients with H1N1 ARDS had lower lymphocyte and leukocyte count than non-H1N1 ARDS. Lower leukocyte count suggests low inflammatory response unlike in bacterial infections. Lymphocytes in blood participate in variety of host defense mechanisms against viral infections. It has been recognized that in-vivo influenza infection transiently depress the number of circulating lymphocytes and their response probably by interfering with 'helper T cell' lymphocyte function [40]. Relative lymphopenia has been observed as a surrogate marker for H1N1 influenza in many studies previously [41-43]. Criswell studied the lymphocyte response to influenza infection in human volunteers and found reduction of all subpopulation of lymphocytes during the illness after inoculation of influenza A virus to volunteers and reduction in B-lymphocytes occur on day 3 who exhibit infection but no changes occurred in uninfected volunteers. This implicates that relative lymphopenia is a reliable surrogate marker for H1N1 influenza infection [44].

Last, although patients with H1N1 ARDS have more severe disease we did not find any difference in mortality rates between H1N1 and non-H1N1 ARDS. Similar findings were noted in studies by Riscili [27] and Samra [38]. In contrast a retrospective Brasilian study done by Nardocci et al., found higher mortality in H1N1 patients compared non H1N1 pneumonia patients (40% vs 20%) [29]. The possible explanation could be due to selection bias as each H1N1 patient were matched at a 2:1 ratio with consecutive cases of Community acquired pneumonia admitted to ICU.

Mortality in ARDS is approximately 34-58% [45]. The past few decades have not seen an improvement in ARDS mortality rates despite of availability of advanced ventilator strategies [46]. We found mortality rate of 35.48% in our study consistent with previous studies. ARDS etiology may affect the prognosis [47] but could not be confirmed in other studies [48, 49]. However we did not find any difference in mortality between different etiologies in our study. Various factors such as cardiac disease [32] cirrhosis [47], obesity [33], thrombocytopenia [50], elevated LDH [32], elevated creatine kinase [51], sepsis [52], old age, length of mechanical ventilation [47], need for invasive ventilation [8], APACHE II scores[53, 54], SAPS II score [47], vasopressor usage [55] were observed as independent predictors of mortality in different studies. APACHE2 score has been a reliable marker for mortality in patients with ARDS. A german study on ARDS patients found APACHE2 score to be the only clinical predictor for mortality [56], similar to our study. We found shorter ICU stay to be protective for mortality possibly due to early transfer out of patients from ICU with less severe disease.

There are several limitations in our study. First our results may not generalized because it was a single centre with a relatively small sample size. There may be many confounding variables which we have not included in our study like fluid management strategy, blood transfusions, changes in ventilator settings made during the course of illness which are known to influence oxygenation in ARDS patients. Our centre was not equipped with advanced rescue ventilation strategies like ECMO, HFOV. Second, we have not used SOFA score to sequentially monitor organ functions. Third, tests for detection of other viruses like respiratory syncytial virus, adenovirus and rhinovirus could not be done due to lack of resources. Last, we have taken single throat swab for H1N1 confirmation but yield of positive PCR for H1N1 with throat swab is around 68% and lower respiratory tract samples is 81% there by misclassifying few cases of H1N1 cases into non-H1N1 category [57].

## Conclusion

Presence of acute clinical symptoms like presence of dyspnea, sore throat and evidence of severe hypoxemia, relative lympho-

penia and leucopenia on lab parameters can be helpful to suspect H1N1 influenza patients in the primary care center as well as an emergency setting which aids the physician for early referral and treatment. On multivariate Cox regression analysis, higher APACHE2 score, shorter ICU stay and need for invasive ventilation was independently associated with higher mortality in patients with ARDS.

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