Journal of Communicable Diseases
Volume 53, Issue 3 - 2021, Pg. No. 89-95
Peer Reviewed & Open Access Journal

Research Article

Critically Ill Patients with H1N1 Pneumonia: Two Year Experience in a Tertiary Level Indian ICU

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DOI: https://doi.org/10.24321/0019.5138.202143

I N F O

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How to cite this article:
Sathe P, Parathody AK, Borse RT. Critically Ill Patients with H1N1 Pneumonia: Two Year Experience in a Tertiary Level Indian ICU. J Commun Dis. 2021;53(3):89-95.

Date of Submission: 2021-06-17
Date of Acceptance: 2021-09-07

A B S T R A C T

*Purpose: T*o learn about the clinical profile, outcome and quality of life and factors influencing these, in critically ill patients with H1N1 pneumonia.

Methods: Retrospective analysis of case files and phone interview of 88patients with confirmed H1N1 pneumonia.

Results: Out of 88 patients, 51 were males. Mean age was 48.23 [± 13.03]. 39 [44.31%] were in the 31-50 years age group and 37 [42.04%] were in the 51-70 age group. Diabetes [n=16] and Hypertension [n=20] were the most common comorbidities. Majority of the patients presented with cough [n=87], breathlessness [n=85] and fever [n=84]. 43 patients had severe ARDS on admission. Mean APACHE II score was 9.6 [± 5.4] Mean SOFA scores 4.99 [± 2.6]. Mean Murray score was 2.37 [± 0.76]. 46 patients [52%] survived. Factors associated with mortality were APACHE score [p=0.00], SOFA score [p=0.00] Murray score, severe ARDS [p=0.00], requirement of vasopressor support [p=0.00] or renal replacement therapy [p=0.00] and incidence of VAP [p=0.039]. Diabetes had a protective effect [p=0.04], as had non-invasive ventilation [p=0.00]. Murray score [p=0.000, SOFA score [p=0.036], initiation of mechanical ventilation [p=0.003] and incidence of VAP [p=0.00] was associated with increased length of stay among the survivors.

Conclusion: Higher lung specific severity scores, severe ARDS, secondary organ failure and VAP were associated with increased mortality. Among survivors, higher Murray and SOFA scores, mechanical ventilation and vasopressor use entailed a longer ICU stay.

Keywords: H1N1, Mortality, Length of Stay, Predictors, Intensive Care

Introduction

The H1N1 virus first came into public attention in 2009 with a pandemic of unprecedented proportions, starting from Mexico and the US, to rapidly spread all over the world.[1] In India, the first case was discovered in May 2009 and it spread rapidly to the rest of the country, and was particularly a problem in Pune city.[2] Although majority of cases suffer only a self-limited influenza like illness, a fraction of the cases develop a severe form of the disease. These patients require intensive care. Due to poor facilities in the under developed peripheral areas in developing countries, many of these patients spend a significant

amount of their initial treatment before getting referred to a higher center.[3,4] Unlike seasonal influenza, the outbreaks of H1N1 pneumonitis tend to involve previously healthy adults in the younger, economically productive age group, this represents a severe blow to the families of the patient in terms of cost, disability or loss of life.[5]

Now H1N1 influenza has become endemic. We present the experience of treating H1N1 cases over the period of two calendar years (2017 & 2018) in a 34 bed multi-disciplinary ICU in a tertiary level health care facility in Pune, Maharashtra, India.

Objective

To understand the clinical profile of H1N1 influenza cases in the community getting admitted to a tertiary level ICU, their course in the hospital, the factors associated with outcome and the impact of the disease on patients' lives.

Materials and Methods

Retrospective analysis of medical records of 88 patients admitted with H1N1 positive influenza [by PCR test] between January 2017 and January 2019 was performed, after getting approval from the ethical committee of the hospital. We looked at the severity of illness, demographic factors, existent co-morbidities, clinical features on presentation, time to first medical contact, time to initiation of antiviral therapy, time to admission at tertiary center, co-infection with influenza B virus, APACHE II, SOFA and Murray scores, requirement, onset and duration of non-invasive ventilation [NIV] & Invasive mechanical ventilation [IMV], Tracheostomy, incidence of hospital acquired infection, intravenous steroid administration, application of ECMO and cytokine adsorption therapy, incidence of renal failure and recovery thereafter. We also looked at patterns of mortality, duration of ICU and hospital stay, and post illness quality of life in survivors. As outcome factors, we looked at either mortality or, for survivors, the duration of ICU stay. Association of these with the above mentioned variables was examined.

Statistical Analysis

Statistical analysis was carried out with SPSS version 18 for windows. Random variables of interest were expressed as mean ± standard deviation and categorical variables as number of counts and percentage. We used chi square test to compare between categorical variables and independent sample T test to compare means for random variables of interest for checking significance of mortality. Bivariate correlation was used to find associations between length of stay and various random variables of interest, and independent sample T test was used for finding significant correlation between categorical variables and duration of stay in ICU for survivors.

Results

51 patients [57.9%] were males and 37 patients were females [Table 1]. Average age was 48 years [± 13 years], ranging from 21 years to 85 years. 44% [n=39] of the patients were in the age group 31-50 years and 42% [n=37] in age group 51-70 years. 16 patients [18%] were diabetic and 20 patients [22.7%] were hypertensive. There were 2 pregnant patients.

Table 1.Population Characteristics

Patient Characteristic	Value
Age (mean ± SD)	48.23 (± 13.03)
Age group [n (%)]	
12-30 years	8 (9.1%)
31-50 years	39 (44.31%)
51-70 years	37 (42.04%)
>70 years	4 (4.5%)
Sex	51 M
	37 F
Co-morbidities (n)	
Diabetes	16
Hypertension	20
Pregnant	2
Obese	3
Ischemic heart disease	3
Malignancy	1
Presenting complaints (n)	
Cough	87
Breathlessness	85
Fever	84
Fatigue	12
Headache	9
Vomiting	5
Loose motions	3
Altered mentation	2
Severity scores [Mean (range)]	
APACHE	9.6 (3-26)
SOFA	4.99 (2-12)
MURRAY	2.37 (0.8-3.8)
PF ratio [n (%)]	
<100	43 (48.8%)
101-200	33 (37.5%)
201-300	12 (13.64%)

Average time to first medical contact was 1.75 [± 1.9] days

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202143

from onset of symptoms. Average delay from symptom onset to positive test for H1N1 pneumonia by RT PCR test was 6.69 [± 3.083] days. 72 patients [81%] had been admitted at another facility before reaching our tertiary center. Average delay from symptom onset to admission at our center: 6.58 [± 3.43] days. Average delay from symptom onset to Oseltamivir initiation was 5.41 [± 2.7] days. Most common clinical features were fever in 84 patients [95.4%], dyspnea in 85 [96.5%] and cough in 87 [98.8%]. Other common symptoms included Fatigue [n=12] vomiting [n=5], Headache [n=90, Loose stools [n=3] and altered mentation [n=2].

APACHE ii score ranged from 2-26; average of 9.6 [± 5.4]. SOFA scores on admission ranged from 2-12 with an average of 5.02 [± 2.6]. Murray score ranged from 0.8-3.8 with an average of 2.37 [± 0.76].

All of our patients had some degree of ARDS at the time of admission. 48.8% patients [n=43] had Severe ARDS [P/F ratio<100] on admission. Disease was moderate [100-200] in 37.5% [n=33] patients 37.5%] and mild [P/F ratio 200-300] in 13.63% [n=12].

66 patients [75%] were initiated on non-invasive ventilation [NIV]. Of these, 28 patients [42.4%] were maintained on NIV alone and 38 [57.5%] required invasive mechanical ventilation. Average delay from symptom onset to NIV initiation was 6.44 days [± 3.54]. Average duration of NIV was 3.38 days [± 2.7]. Average NIV duration was 3.71 days [± 2.6] in patients who were managed on NIV alone. 57 [64.7%] patients required invasive ventilation. Of these, 38 patients [66.7%] required intubation after an NIV trial, whereas 19 patients [33.3%] required direct intubation. Initiation of invasive mechanical ventilation was at an average of 7.15 days [± 4.27] from onset Average duration of IMV was 13.5 days [± 2.12]. 3 patients were managed without any form of ventilator support despite mild ARDS.

Table 2.Initial Treatment Characteristics

Onset to first medical contact (mean days)	1.75 (± 1.96)
Onset to positive test (mean days)	6.69 (± 3.1)
Onset to admission at tertiary center (mean days)	6.55 (± 3.43)
Onset to oseltamivir initiation (mean days)	5.42 (± 2.71)
Number of patients initially admitted at periphery [n (%)]	72 (81.8%)

Vasopressors were required in 52 [59%] patients. Intravenous steroids were used in 39 [44.31%] patients. 36 patients [40.1%] had an organ failure in addition to respiratory and 14 [15.91%] patients had two additional organ failures. Most common organ failure was cardiovascular failure in 52 patients [59%] followed by renal failure in 17 [19.3%] Extra corporeal membrane oxygenation was used in 6 patients. Extracorporeal cytokine adsorption therapy was used in 5 patients. There were 21 instances of ventilator associated pneumonia and 15 incidences of central line related infections. ICU stay on average was 12.09 [± 9] days [Minimum 1, maximum 69 days]. Hospital stay was 15.04 days [± 10] on average [Minimum 1, maximum 91 days] Among the survivors, mean ICU stay was 12.57 [± 13.69, range 1-62]days and mean hospital stay was 18.46 days [± 18.29, range 3 to 91].

46 [52%] patients survived and were shifted out of ICU and discharged to home subsequently. 37 [42%] patients expired during their ICU course. 5 patients took discharge against medical advice due to various reasons and expired subsequently in the course of the same illness. The subgroup mortality for severe, moderate and mild ARDS cases was 69%, 30% and 16% respectively.

We managed to follow up with 40 families [86.9%] out of the 46 survivors. 6 patients could not be contacted. Out of 40 patients & families that we were able to contact, two patients had died within the 2 months following discharge, reportedly to due to respiratory tract infections. Details of the latter could not be obtained. Three patients reported some restriction in activities of daily living at 1 year post illness. Two patients had two respiratory tract infections in the subsequent year, the remaining 33 were able to return to their previous levels of activity. Out of the entire cohort, 14 families of patients [15.9%] have taken vaccination against influenza. One patient, a survivor, reported two others in the family contracted H1N1 infection during his illness.

APACHE score was found to be higher on average among the non-survivors as compared to the survivors [12.28 ± 5.84 vs. 6.63 ± 2.66; p=0.00] [Table 3]. Similar associations were found for SOFA score [6.62 ± 2.696 vs. 3.57 ± 1.41; p=0.00] and Murray score [p=2.82 ± 0.63 vs. 1.95 ± 0.62; p=0.00], respectively. By logistic regression, it was found that Murray score correlated best with mortality [OR 7.89; 95% CI 3.29-18.9], compared to APACHE and SOFA scores with ORs 1.491 [95% CI 1.24-1.793] and 1.996 [95% CI 1.47-2.70] respectively. Other factors found to be associated with significant mortality were severe ARDS [p=0.00], increasing number of organ failures, as judged by use of vasopressors and renal replacement therapy or both [p=0.00]. Incidence of ventilator associated pneumonias were also found to have a significant association with mortality [p=0.039]. Interestingly, diabetes mellitus as a co-morbidity was found to have a slight protective effect towards mortality [p=0.04]. Also, application of non-invasive ventilation was found to have a protective effect [p=0.00].

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202143

Table 3.Comparison of Survivors vs. Non-Survivors

Parameter	Survivors	Non-survivors	p value
Age	45.8 (± 13.9)	50.8 (± 11.7)	0.077
Sex	24 (47.1%)	27 (52.9%)	0.34
Diabetics	12 (75%)	4 (25%)	0.04
Hypertensive	10 (50%)	10 (50%)	0.82
Onset to first medical contact (days)	1.7 (± 2.2)	1.79 (± 1.73)	0.831
Onset to positive test(days)	6.98 (± 3.5)	6.36 (± 2.6)	0.35
Onset to reaching tertiary center	7 (± 3.8)	6.1 (± 2.9)	0.23
Onset to oseltamivir administration	5.52 (± 2.8)	5.29 (± 2.6)	0.69
APACHE	6.63 (± 2.7)	12.9 (± 5.8)	0.00
SOFA	3.57 (± 1.4)	6.62 (± 2.7)	0.00
MURRAY	1.95 (± 0.6)	2.82 (± 0.63)	0.00
Severe ARDS	13 (30.2%)	30 (69.8%)	0.00
Vasopressor use	14 (27.5%)	37 (72.5%)	0.00
Renal replacement therapy	1 (5.9%)	16 (94.1%)	0.00
Intravenous steroid use	18 (46.2%)	21 (53.8%)	0.31
Incidence of VAP	7 (33.3%)	14 (66.7%)	0.048

The risk of renal failure requiring renal replacement therapy was associated with P/F ratio < 100 [p=0.002] requirement of invasive mechanical ventilation [p=0.000], higher severity scores as in APACHE [p=0.000], SOFA [p=0.001] or MURRAY [p=0.000] scores. Initiation of non-invasive ventilation had a protective effect against renal failure [p=0.025]. Similarly, cardiovascular system involvement was found to be significantly higher in patients with PF ratio < 100 [p=0.000] higher severity scores as in APACHE [p=0.000], SOFA [p=0.000] or MURRAY [p=0.000] scores, those with requirement of invasive mechanical ventilation [p=0.000]. Here also initiation on NIV was found to have a protective effect [p=0.008]. Murray score outperformed SOFA and APACHE scores in terms of association with both renal failure OR 5.58 [2.193-14.23] vs. 1.36 [1.11-1.67] & 1.19 [1.07-1.32] and cardiovascular failure: OR 9.124 [3.4-23.9] vs. 1.7 [1.36-2.32] & 1.2 [1.08-1.37] respectively.

Among the survivors, factors associated with increased length of stay in the ICU were: Murray score [p=0.00], SOFA score [p=0.036]. Initiation of invasive mechanical ventilation entailed a longer ICU stay [p=0.00], as did use of vasopressors [p=0.003] and incidence of ventilator associated pneumonia [p=0.00].

Discussion

H1N1 pneumonia, after the first epidemic of 2009 has evolved into a serious recurring problem. Finding correlates of severe disease and therefore mortality is important to the planning of strategies to combat the disease.[6] We conducted a retrospective analysis of H1N1 positive pneumonia patients admitted to our tertiary level ICU over a period of two years in an attempt to assess the factors contributing to mortality and morbidity among these patients. We hope to provide further insight into this condition that causes a yearly flux of critically ill patients to ICUs across the country.

We did not find a definite association between age or sex of patients and outcome factors. Such correlations have been found in a few studies in the past.[7,8] Most of our patients were among the active adult age group. This correlates with the findings of many previous studies on the disease, and is different from the normal pattern of seasonal influenza.[9,10] It has been postulated that this may be explained by the presence of cross-reacting antibodies in the blood of older age groups.[11] Regardless of the cause, this aspect gives H1N1 influenza a serious economic impact.

Diabetes and Hypertension figured as the most common pre-existing conditions in our population.[4,10] There were fewer cases of bronchial asthma than in previous studies. In our study diabetes was found to have a statistically significant protective effect towards mortality. This may be due to the presence of attenuated cytokine storm in these patients; a phenomenon which has been previously described.[12] We found no association on mortality or length of stay with any other condition, including pregnancy, which has been earlier described.[13]

Average time to seek medical care and oseltamivir initiation were found to be comparable to previous studies in the Indian scenario, and more than the recommended time frame, but we could not find any significant bearing of this on mortality.[3,13,14] The time to be referred to tertiary center was found to be less in survivors who had longer ICU stay, this could be a reflection of more severe patients getting referred sooner.

Fever, cough and breathlessness were the predominant complaints of patients, similar to past pandemics of acute respiratory illness. A greater proportion [96.5%] of patients

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202143

presenting to us were dyspneic, which is probably explained by the greater proportion of severe and moderate ARDS in our study population [48.8% & 37.5%, respectively].[10,15]

APACHE II, SOFA and Murray scores were all associated with increased mortality. Similar associations have been observed previously.[14,16] The latter two were also associated with increased length of stay among the survivors. All of the above scores are ways of looking at the severity of illness in critically ill patients and predicting the severity and/or mortality. APACHE II uses age, initial values of 12 physiologic variables, and previous health status to give a score denoting a general measure of severity of disease. An increasing score correlates with the risk of mortality for ICU admissions.[17] SOFA [Sequential Organ failure Assessment] score used a scoring system for six physiological variables to generate a total score which is found to correlate with mortality in ICU patients.[18] The observed mortality in our population was more than that predicted by APACHE or SOFA scores at admission. This may be explained by the fact that these multi-organ system predictors do not work as accurately in these cases of severe single organ disease. The Murray Score is slightly different in that it was developed to describe patients with lung injury. It uses a combination of lung compliance, chest X-ray findings, positive end expiratory pressure values and PF ratio to generate a score used to predict severity of disease, and has been used to triage patients for ECMO therapy in the past.[19,20] Since all our patients were critically ill in the first place due to their acute lung injury, the better fit of Murray Score to our patients stands to reason. Treatment with intravenous steroids has been associated with worse outcomes in literature.[16, 26] In our study, although mortality was more among the patients receiving steroids, the correlation was not statistically significant. Although 27 [30.6%] of our patients were eligible for ECMO as per available evidence,[19,20] the therapy could be successfully initiated in only in 6 of these patients, due to various reasons. 6.81% of original population]. Use of ECMO or ECAD therapies was not found to have a significant effect on mortality in our study.

The significant fraction of patients that had severe ARDS by the ARDS Berlin criteria also showed a higher risk of mortality. Incidence of organ failures, which in our case were cardiovascular and/or renal failure, both increased the risk of death. Such association has been previously described, and stands to reason. It underscores the risk of H1N1 pneumonitis progressing to multi organ dysfunction and increasing the likelihood of mortality.[4,14,16,21] Cardiovascular involvement in H1N1 pneumonitis has been previously described due to various causes.[21-24] The risk of cardiovascular failure was more in severely ill patients receiving ventilatory support in the form of invasive ventilation, higher severity of ARDS, higher APACHE, SOFA or Murray scores. Similarly the risk of renal involvement was also found to be higher in the sicker patients, those with higher severity scores, and severe ARDS, and requiring invasive ventilatory support. Most of the patients requiring renal replacement therapy did not recover their renal function, consistent with previously observed patterns.[8,15,24,25]

Mortality from H1N1 pneumonitis has been variously reported in literature over a wide range, predominantly due to the difference in the severity of illness in the populations under study.[4,13,14,27,28] We had a relatively higher mortality rate, reflecting the high proportion of severe ARDS patients making up our study population.

On follow up most of the survivors were found to be enjoying good health. Vaccination can be an effective tool against the spread of infection.[30,31] Despite the seriousness of the illness and the educational campaigns carried out at various levels, penetration of vaccination in the general populace remains woefully low, and is borne out by the current data.

Our study has several limitations. Our study population included only patients admitted to the ICU, making our results pertinent to the worst cases of H1N1. Our population is composed entirely of adults. The data collection was retrospective in nature. There was variability in treatment where use of steroids was concerned. Due to the comparatively smaller size, we could not effectively perform certain advanced statistical analyses with our data. Formal assessment of post-illness status could not be done.

Conclusion

In our study, we tried to describe the clinical profile of patients getting admitted to the ICU with severe H1N1 pneumonia and to find the factors influencing the mortality and length of stay among this population. The patients were mainly in the young adult and middle-aged group. There was significant delay in the administration of antivirals, confirmation of diagnosis and also in reaching the tertiary center. Observed mortality was more than that predicted by routine ICU severity scores. Cardiovascular and renal systems were the most common secondary organ failures observed. The risk factors for mortality included higher APACHE, SOFA and Murray scores, severe ARDS, secondary organ failure, incidence of ventilator associated pneumonia. Murray score correlated best with observed mortality. Among survivors, higher Murray and SOFA scores, invasive mechanical ventilation and vasopressor use were associated with a longer ICU stay.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest: None

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ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202143

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ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202143