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A Comparative Study of the Survivors and Non-Survivors of Acute Respiratory Distress Syndrome

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ABSTRACT

Acute respiratory distress syndrome (ARDS) is a life threatening condition in which respiratory failure occurs due to lung injury caused by various etiological factors. Acute hypoxemic respiratory failure as occurs in ARDS requires positive pressure ventilation. ARDS is a major cause of morbidity and mortality; and it also leads to major expenditure in intensive care units. This is a comparative hospital based observational study conducted over a period of one year in an emergency ICU to compare the clinical profile of survivors and non-survivors of ARDS. Included in the study were adult patients who fulfilled the criteria for ARDS according to the Berlin Definition of 2012. The study included 44 patients with ARDS, which was 6.3% of the total number of patients admitted to emergency ICU. There was no significant difference in relation to age among survivors and non-survivors. Non-pulmonary sepsis was the most common cause of ARDS (29.5%) followed by aspiration (22.7%), shock (18%), pneumonia (14%), pancreatitis (11%), malaria (9%) and major trauma (7%). The mortality in our study was 54.54%. The mean initial PaO_2/FiO_2 ratio in survivors (162.8±41.89) was more than that in non-survivors (88.9±7.71); the difference being statistically significant ($p<0.0001$). Out of the non-survivors, 54% had sepsis as the cause. Non-survivors have lower oxygenation ratio at presentation and more number of organ dysfunction.

***Keywords**: ARDS, Acute lung injury, Mechanical ventilation*

INTRODUCTION

The acute respiratory distress syndrome was first described in a study by Ashbaugh and Petty in 1967.[1] Pathologically it is characterized by diffuse alveolar damage, alveolar capillary leakage, and protein rich pulmonary edema leading to gas exchange abnormalities and altered lung mechanics. The most common causes are sepsis, pneumonia, aspiration, trauma, pancreatitis, multiple blood transfusions, smoke or toxic gas inhalation, and certain types of drug toxicity.[2]

Acute hypoxemic respiratory failure as occurs in ARDS requires positive pressure ventilation for achieving desired oxygenation of blood as was first reported in the study by Ashbaugh et al. in 1967.[1] However, care must be taken not to exacerbate the lung injury by causing stretching and over distension of alveoli by injudicious mechanical ventilation.[3, 4] To protect the lungs from further injury certain lung protective measures are adopted, e.g. the restriction of tidal volume, limiting plateau pressure in lungs and application of positive end expiratory pressure.[4, 5] Substantial variation in mortality in ARDS can occur depending upon the underlying disorder. The risk of death

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appeared to be the highest in patients with ARDS with sepsis, intermediate in patients with pneumonia, aspiration and lowest in those with trauma.[6]

The incidence of ARDS varies widely. Estimates from prospective cohort studies in the United States ranged from 64.2 to 78.9 cases per 100,000 person-years.[7,8] Estimates from Northern Europe (17 cases/100,000) and Australia and New Zealand (34 cases/100,000) are much lower.[9,10] Reasons for such large variation in ARDS incidence are unclear, and may be due to differences in demographics, variability of identification of the disorder by health care providers and different criteria used for diagnosis.

The mechanism of lung injury may be direct as occurs in aspiration, inhalational injury, pneumonia, lung contusion, near-drowning, fat embolism, etc. or indirect as in sepsis, major trauma, acute pancreatitis, severe burns, shock, drug overdose and multiple transfusions.[2] Controversies exist in the definition of ARDS. Murray's expanded definition of ARDS[11], American European Consensus Conference (AECC) criteria of 1994[12] Delphi consensus criteria and recently the Berlin definition[13] are the most commonly adopted definitions of ARDS. The new definition categorized ARDS into mild, moderate and severe categories based on the PaO_2/FiO_2 ratio with PEEP or CPAP $\geq$5 cm H_2O.

The pathological features of ARDS are described as evolving through three phases, viz. an exudative phase, a proliferative phase and, lastly, a fibrotic phase. The degree of fibrosis is a key predictor of outcome.[14] The major features of ARDS on chest radiography comprise bilateral, widespread, patchy, ill-defined lung opacification usually without cardiomegaly and upper zone blood diversion. The opacities progress in severity to produce confluent airspace opacification with variable distribution, but usually all lung zones are involved both centrally and peripherally.

In a comparative study by Puybasset et al. it was seen that end-expiratory lung volume and functional residual capacity (FRC) were reduced in ARDS patients in comparison to healthy volunteers.[15] Collapse occurs mainly in the dependent lung, where the superimposed weight from above is greatest.[16] Measurements of pulmonary mechanics in mechanically ventilated patients with ARDS showed decreased static lung compliance as a consequence of loss of ventilated lung.[17] The airflow resistance is also increased in ARDS as a result of decreased lung volume, bronchospasm caused by inflammatory mediators, and can contribute to derangement of lung mechanics.[18] Survival of patients with ARDS is linked to both non-pulmonary organ failure and recurrent infection.

Conventional ventilation is based on the strategy of maintaining the lowest positive end-expiratory pressure (PEEP) for desired oxygenation, with a tidal volume of 10-15 ml/kg body weight and normal $PaCO_2$ level.[19] In the ARMA trial which was a randomized, controlled, multicenter clinical trial designed to compare a lower tidal volume with a higher tidal volume ventilatory strategy, a lung protective ventilation strategy was recommended involving a restriction of tidal volume to less than 6ml/kg predicted body weight and a maximum plateau pressure (Pplat) of 30 cm H_2O and application of positive end-expiratory pressures, permissive hypercapnia, and preferential use of pressure-limited ventilatory modes.

MATERIALS AND METHODS

This was a comparative hospital based observational study, involving patients admitted to emergency ICU of Gauhati Medical College and Hospital over a period from August 2014 to July 2015. All patients fulfilling the criteria of ARDS according to the Berlin definition were included in the study. Patients of chronic obstructive airway disease, chronic interstitial lung disease, active pulmonary tuberculosis, heart failure, decompensated chronic liver disease, end stage renal disease and patients of less than 18 years of age were excluded from the study.

The initial ventilator parameters viz. ventilator mode, tidal volume, respiratory rate, peak inspiratory pressure, plateau pressure, positive end expiratory pressure (PEEP), fraction of oxygen in inspired air (FiO_2), were recorded after 20 minutes of initiating mechanical ventilation. The FiO_2 value required to maintain SpO_2 between 88-95% at a minimum PEEP level of 5 cm H_2O was recorded. If oxygen saturation was not maintained in the desired range than PEEP and FiO_2 titration were set according to the $PEEP/FiO_2$ tables of the ARDS Network protocol. Arterial blood gas analysis was done after 20 minutes of initiation of mechanical ventilation and findings were recorded. Patients were then categorized as having mild, moderate or severe ARDS based upon the PaO_2 / FiO_2 ratio according to the Berlin definition. Arterial blood gas measurements were repeated every 24 hours. Chest radiograph findings were recorded every day till weaning. Ventilator parameters, tidal volume, plateau pressure, PEEP, static compliance, respiratory rate,

FiO_2 were recorded every 24 hours after the initiation of mechanical ventilation. Patients were monitored daily for signs of non-pulmonary organ failure. Organ failure was assessed according to the Sequential Organ Failure Assessment (SOFA) score criteria.

Results of numerical variables were reported as Mean (± SD), relative risks with 95% confidence intervals (CIs). Categorical variables were reported as percentage. Student t test and Kruskal-Wallis test was applied as test of significance for numerical data and Fisher Exact test for categorical data. SPSS 16.0 software was used for statistical analysis.

RESULTS

The number of patients with ARDS included in this study was 44 which were 6.3% of the total number of patients admitted to emergency ICU during the study period. There were 20 survivors (45.46%) and 24 non-survivors (54.54%).

The frequency distribution of etiological factors of ARDS is shown in **Table 1**. Non-pulmonary sepsis is found to be the most frequent cause in 13 cases (29.5%), followed by aspiration (22.7%) and shock (20.4%).

Table 1 Frequency Distribution of etiological factors of ARDS seen in this study

Etiological Factor	Frequency (n=44)
Non-pulmonary sepsis	13 (29.5%)
Aspiration	10 (22.7%)
Shock	9 (20.4%)
Pneumonia	6 (13.6%)
Acute Pancreatitis	5 (11.3%)
Malaria	4 (9%)
Major trauma	3 (7%)
Fat Embolism	2 (4.5%)
Anaphylaxis	1 (2.25%)
Drug overdose	1 (2.25%)

Table 2 shows the cause wise distribution of mortality, the highest mortality being in cases of Non-pulmonary sepsis (76%).

Table 2 Cause wise distribution of mortality in ARDS

Cause	Total patients (n=44)	Death
Non-pulmonary sepsis	13	10 (76%)
Pneumonia	6	4 (67%)
Aspiration	10	3 (30%)
Acute pancreatitis	5	3 (60%)
Malaria	4	2 (50%)
Major Trauma	3	1 (33%)
Fat Embolism	2	0 (0%)
Drug overdose	1	1 (100%)
Anaphylaxis	1	0 (0%)

A comparison of various factors among survivors and non-survivors is shown in **Table 3**.

Table 3 Comparison of the various contributing factors among survivors and non-survivors

	Survivorsn =20	Non-survivorsn =24	p value (Unpaired t-test)
Age (Mean±SD)	39.25± 17.39	41.3±11.45	0.644
Initial PaO_2/FiO_2 (Mean±SD)	162.8± 41.89	88.9± 7.71	<.0001
Static compliance (Cs)ml/cm H_2O (Mean±SD)	27.2±7.76	25.7±5.83	0.47
Number of non-pulmonary organ failure (Mean±SD)	2.75±1.61	3.87±1.36	0.0092

Table 4 shows comparison of mortality in patients with sepsis and other causes. Sepsis was found to be associated with the highest number of deaths.

Table 4 Comparison of mortality in patients with sepsis and other causes

	Dead	Alive	Total	Relative Risk	p value (by Fisher exact test)
Sepsis	13 (29.5%)	3 (6.8%)	16 (36.4%)	2.1(95% CI 1.2 to 3.5)	0.011
Other	11 (25%)	17 (38.6%)	28 (63.6%)		
Total	24 (54.5%)	20 (45.4%)	44 (100%)		

DISCUSSION

The incidence of ARDS in patients admitted to emergency department reported by various authors range from 8.7% (Goyal et al.)[20] to 7% (Elie-Turenne et al.)[21] and 6.8% (Gajic et al.).[22] In our study this was found to be 6.3% of the total number of patients admitted to emergency ICU.

Non-pulmonary sepsis was found to be the most common cause of ARDS (29.5%) followed by aspiration (22.7%), shock (20.4%), pneumonia (13.6%), pancreatitis (11%), malaria (9%) and major trauma (7%). The finding of sepsis as the major cause was also reported by Gajic et al.[22], Rubenfeld et al.[7], while Bhadade et al. reported malaria in (27.6%) and leptospirosis (20.7%) as important causes of ARDS.[23]

In this study 76% of patients with non-pulmonary sepsis and 67% of the pneumonia patients with ARDS died. Rubenfeld et al. reported mortality rate varying from 24.1% among patients with severe trauma to 40.6% among patients with severe sepsis.[24]

The mean age of the survivors was 39.25±17.39 years and that of non-survivors was 41.3±11.45 years, which was not statistically significant (p = 0.644). In a study by Rubenfeld it was seen that mortality increased with age from 24% (15 to 19 years) to 60% in patients 85 years of age or older (P<0.001).[7] Suchyta et al. found significant increase in mortality in ARDS with age more than 65 years.[25] But Singh et al. found no statistically significant difference in the mean age of survivors and non-survivors.[26]

The mortality in our study was 54.54%. Agarwal et al reported 47.8% hospital mortality rate for ARDS.[27] There had been a decreasing trend in mortality in ARDS patients which might be attributed to the widespread adoption of the lung-protective mechanical ventilation strategies. The ARMA trial of ARDS Net group showed mortality of 21% in those with lung-protective mechanical ventilation vs. 40% in those with conventional ventilation.[7] Erickson et al. observed that mortality in ARDS was 35% in 1996-1997 and declined to a level of 26% in 2004-2005.[28] In 2005 Rubenfeld et al. reported in-hospital mortality rate of 41.1% for ARDS.[8] In a recent prospective, multicenter observational study by Villar et al.[29], it was seen that despite use of lung protective ventilation, ICU mortality of ARDS patients was still more than 40%.

In our study the mean initial PaO_2 /FiO_2 ratio in survivors was 162.8±41.89 and in non-survivors it was 88.9± 27.71. The difference was statistically significant (p <0.0001). The ARDS task force conducted a meta-analysis of 7 clinical trials and prepared the draft of the Berlin definition in which they observed that mortality in mild ARDS was 27%, in moderate ARDS 32%, and in severe ARDS 45% and the difference was statistically significant (p<.001). Esteban et al.[30] reported mortality of 25% in the group of patients with PaO_2/FiO_2 of 200-300, 31% with PaO_2 /FiO_2 150-199, 47% with PaO_2 /FiO_2 of 100-149 and 83% with PaO_2 /FiO_2 of less than 100. Villar et al. observed that PaO_2/FiO_2 ratio at the time of ARDS identification had an inverse relationship to mortality.[29]

The static lung compliance (Cs) at initiation of mechanical ventilation was 27.2±7.76 ml/cm H_2O in survivors and 25.7±5.83 ml/cm H_2O in non-survivors in this study. The difference is not statistically significant. Kangelaris et al.[31] observed that there was no statistically significant difference in the lung compliance among survivors and non-survivors of ARDS. Changes in the tidal volume, inspiratory flow rates, and level of PEEP can improve compliance.

In this study all the non-survivors had more than one non-pulmonary organ dysfunction. In the survivors the mean number of non-pulmonary organs in failure was 2.75 ± 1.61 and in non-survivors it was 3.87±1.36. Unpaired t-test was done and the one-tailed p value was found to be 0.0092 which is statistically significant. Villar et al.[29] observed that more the number of failing organs, the greater was the mortality in ARDS patients. Suchyta et al. also observed similar findings.[25]

In this study the percentage of patients with sepsis (pulmonary and non-pulmonary) at presentation was 36.4% (16 out of 44 patients). Out of the non-survivors 54% patients with sepsis died, which was found to be twice more than patients without sepsis (Relative risk 2.1 with 95% CI 1.2 to 3.5; p =0.011). Montgomery et al. in a prospective study reported that majority of late deaths were related to sepsis, and 73% of those who died after 3 days met criteria for sepsis syndrome.[32] Suchyta et al. also reported similar findings.[25]

CONCLUSION

ARDS is associated with several clinical conditions ranging from trauma to sepsis. Non-survivors have lower oxygenation ratio at presentation and more number of organ dysfunction. Sepsis was associated with the highest number of deaths.

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(4) All author(s) have reviewed the final version of the above manuscript and approve it for publication.

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