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Factors associated with the development and outcome of acute respiratory distress syndrome: A prospective observational study

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Background: Acute respiratory distress syndrome (ARDS) is a life-threatening disorder of the lungs associated with high mortality. This work was done to determine the risk factors for the development of ARDS and the predictors of adverse clinical outcomes in patients with ARDS.

Methods: This hospital-based prospective observational study included 96 patients who fulfilled Berlin's criteria for ARDS. Their demographic, vital, and biochemical parameters were recorded and the etiology of ARDS in each patient was determined along with the severity of the disease and corroborated with the survival and outcome of patients.

Results: Male predominance was observed (62.5%). Sepsis (45.8%) was overall the most common cause while pneumonia (41.6%) was the most common direct cause of ARDS. Abdominal pain, altered sensorium, and low mean arterial pressure (MAP) were associated with poor outcomes ($p < 0.05$ each). Increased mortality was associated with low hemoglobin ($p = 0.004$), low hematocrit ($p = 0.015$), thrombocytopenia ($p = 0.021$), raised serum creatinine ($p = 0.047$), hyperbilirubinemia ($p = 0.020$), raised serum alkaline phosphatase ($p = 0.011$), hypoalbuminemia ($p < 0.001$), raised d- dimer ($p = 0.011$), and high illness severity scores like sequential organ failure assessment (SOFA) score ($p = 0.004$) and acute physiology and chronic health evaluation (APACHE) score ($p = 0.002$). The mortality rate of ARDS was 58.3%.

Conclusions: Sepsis and pneumonia are the most frequent causes of ARDS associated with high mortality. The presence of abnormal clinical and biochemical parameters has a significant effect on the outcome of patients with ARDS.

Keywords:

Acute respiratory distress syndrome; Predictors; Development; Clinical outcome; SOFA score;

Introduction

Acute respiratory distress syndrome (ARDS) is a disorder of diverse etiologies described as a consistent, recognizable pattern of injury of the lung which causes an acutely devastating form of inflammatory lung injury with a high mortality rate in a short period of time and remarkable long-term morbidity among survivors[1].

ARDS is associated with acute onset of hypoxemia i.e., within 7 days of known clinical insult with bilateral lung infiltrates seen on chest skiagram, that occurs due to the injury to the parenchyma of lungs causing alveolar epithelial injury or injury to pulmonary vasculature causing lung endothelial injury[2-4] The incidence of ARDS varies from region to region, which ranges from 1.5 to 79 cases of ARDS per lakh population. Studies in the Indian population report an incidence rate of 11.4% among ventilated patients.5-8

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Mortality due to ARDS remains high and depends on the region, intensive care unit (ICU) type, etiology, ARDS definition, etc. With an increase in severity of ARDS, the mortality increases from 27% to 45%.9-12 The mortality rate of the Indian population in western and northern regions is 57%13 and 47.8%14, respectively.

There are approximately 60 known causes of acute respiratory distress syndrome. The causes of ARDS are divided into direct or indirect, also known as pulmonary or extra-pulmonary. Both medical and surgical causes contribute to ARDS. Common causes include direct causes such as pneumonia, inhalational injury, gastric contents aspiration, and drowning, and indirect causes like pancreatitis, sepsis, non-cardiogenic shock, severe burns, major trauma, and multiple transfusions. Among the direct causes of ARDS, aspiration, pneumonia, and infections are predominantly seen, while systemic sepsis remains the primary indirect cause of acute respiratory distress syndrome.13, 15-17

Risk factors such as advanced age, partial pressure of arterial oxygen (PaO2)/ fraction of inspired oxygen (FiO2) or PF ratio, oxygenation index, need for mechanical ventilation, development of non-pulmonary organ dysfunction such as liver cirrhosis, hypoalbuminemia, presence of pulmonary ARDS, length of hospital stay, and severity illness scores such as acute physiology and chronic health evaluation (APACHE) score and severity scores like sequential organ failure assessment (SOFA) score are the predictors of mortality in ARDS patients.18, 19

This study aimed to analyze the factors associated with the development and outcome of ARDS of varying etiologies.

Materials and methods

This prospective observational study was conducted in a tertiary care institute in Uttarakhand, India from July 2021 to June 2022. The study was approved by the institutional ethics committee and was in accordance with the principles of the Declaration of Helsinki. Patients with ARDS were included in the study after obtaining informed written consent from the patients or next of kin if a patient was not able to give consent due to severe illness.

The study included 96 patients above the age of 18 years who fulfilled Berlin's criteria for ARDS which include, acute onset within 7 days of a clinical insult by known risk factor or new or aggravating symptoms, chest radiograph suggestive of bilateral infiltrates which is not completely explained by pleural effusion, lung collapse or pulmonary nodules, hypoxemic respiratory failure not explained by heart failure and fluid overload, and PF ratio ≤300 with a continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) value of minimum 5 cm of water.5, 20

Parameters such as demographic profile (age and gender), clinical manifestations, co-morbidities, vital parameters [including temperature, pulse, heart rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP)], the need of vasopressor, the severity of ARDS based on PF ratio, baseline laboratory parameters, ventilation requirement (invasive/non-invasive), and length of hospital stay were documented. Illness severity scores such as APACHE score and SOFA score were recorded within 24 hours of hospital admission.

The etiology of ARDS was determined based on clinical manifestations, physical examination findings, radiographic assessment, and appropriate biochemical and microbiological investigations. The etiology of ARDS was classified as direct or pulmonary and indirect or extra-pulmonary.

Patients were assessed twice during the hospitalization-first at the time of admission and again at the time of discharge or at the time of death. The patients were categorized into two groups, in which those patients who completely recovered and were discharged were considered as the survivor group and those patients who did not recover or died or were discharged against medical advice were included in the non-survivor group.

Data Management and Statistical Analysis

Results were analyzed by using SPSS Software version 22. The one-sample Kolmogorov-Smirnov test was employed to determine whether the data sets differed from a normal distribution. Student's unpaired t-test was applied for comparing the normally distributed quantitative data between the two groups, whereas, non-normally distributed data were analyzed using the Mann-Whitney U test. The Chi-square test was used for testing differences between proportions or associations between various variables. A p-value < 0.05 was taken as statistically significant.

Results

Out of 96 patients, 42 (43.7%) patients were above the age of 60 years. Among patients who did not recover, a maximum (28.6%) were from the age group of 61 to 70 years. No significant association was seen between the age of patients and the outcome of ARDS ($p = 0.680$). The majority of patients were male, with a male-to-female ratio of 1.6:1. Mortality was observed among 35 (62.5%) males and 21 (37.5%) females. No significant association was seen between gender and the outcome of patients with ARDS ($p = 0.823$).

Sepsis was overall the most common cause of ARDS while pneumonia was the most common direct cause of ARDS. Among patients who survived, pneumonia, sepsis, and pancreatitis were present in 27.5%, 25%, and 12.5% of patients respectively. Among patients who did not survive, sepsis, pneumonia, pancreatitis, and aspiration were present in 60.7%, 51.7%, 7.1%,

and 5.3% of patients respectively. Pneumonia and sepsis had a significant association with the outcome (p = 0.029 and 0.002 respectively). Comorbidities were present in 75% of survivors and 66% of non-survivors. Hypertension (32.2%) and type 2 diabetes mellitus (29.1%) were the most common comorbidities, followed by chronic obstructive pulmonary disease (COPD) (15.6%) and chronic kidney disease (CKD) (10.4%) (Table 1).

Table 1: Demographic profile, etiology, and co-morbidities of ARDS survivors and non-survivors

Parameters	Number of patients (%)		p-value
	Survivors (n=40)	Non-survivors (n=56)	
Demographic profile			
Age			
<60 years	21 (52.5)	33 (58.9)	0.680
>60 years	19 (47.5)	23 (41.0)	
Gender			
Males	25 (62.5)	35 (62.5)	0.823
Females	15 (37.5)	21 (37.5)	
Environmental factors			
Smoking			
Yes	21 (52.5)	31 (55.3)	1
No	19 (47.5)	25 (44.6)	
Alcohol use			
Yes	16 (40)	23 (41.0)	0.920
No	24 (60)	33 (58.9)	
Etiology of ARDS			
Pulmonary			
Pneumonia	11 (27.5)	29 (51.7)	0.029
Aspiration	0 (0)	3 (5.3)	0.263
Non-pulmonary			
Sepsis	10 (25)	34 (60.7)	0.002
Pancreatitis	5 (12.5)	4 (7.1)	0.483
Comorbidities			
Chronic kidney disease	2 (5)	8 (14.2)	0.185
Chronic obstructive pulmonary disease	8 (20)	7 (12.5)	0.475
Type 2 diabetes mellitus	11 (27.5)	17 (30.3)	0.920
Hypertension	15 (37.5)	16 (28.5)	0.483
Coronary artery disease	7 (17.5)	0 (0)	0.001
Chronic liver disease	0 (0)	6 (10.7)	0.078
Cerebrovascular accident	1 (2.5)	5 (8.9)	0.395
Pulmonary tuberculosis	2 (5)	1 (1.7)	0.568
Malignancy	2 (5)	1 (1.7)	0.568
Rheumatoid arthritis	0 (0)	3 (5.3)	0.263
Hypothyroidism	1 (2.5)	0 (0)	0.416
Gout	1 (2.5)	0 (0)	0.416
Obstructive sleep apnea	1 (2.5)	0 (0)	0.416
Post renal transplant	0 (0)	1 (1.7)	1
Hepatitis C	0 (0)	1 (1.7)	1

The most common clinical manifestations were shortness of breath (55.2%), fever (39.5%), altered sensorium (23.9%), abdominal pain (21.8%), vomiting (18.7%), and cough (16.6%). Abdominal pain and altered sensorium were present in a significantly higher number of patients among non-survivors than survivors (p = 0.023 and p < 0.001 respectively). The mean arterial pressure (MAP) was significantly lower among non-survivors than survivors (p = 0.049). Vasopressors were needed in 32.5% of survivors and 46.4% of non-survivors. The association between the need for vasopressor support and outcome was statistically not significant (p = 0.247).

The majority of patients had mild (43.7%) to moderate (39.5%) severity of ARDS. Among non-survivors, 21.4% of patients had severe ARDS followed by moderate (41%) and mild (37.5%) forms of ARDS. No significant association was seen between the severity of ARDS and mortality (p = 0.212). Mechanical ventilation was required in 82.5% of survivors and 94.6% of non-survivors. The association between the requirement for ventilation and the outcome was found to be statistically not significant (p = 0.087) (Table 2).

Table 2. Clinical parameters of ARDS survivors and non-survivors

Parameters	Number of patients (%)		p-value
	Survivors (n=40)	Non-survivors (n=56)	
Clinical manifestations			
Fever	14 (35)	24 (42.8)	0.571
Shortness of breath	21 (52.5)	32 (57.1)	0.806
Sore throat	6 (15)	2 (3.5)	0.063
Cough	10 (25)	6 (10.7)	0.115
Hemoptysis	0 (0)	1 (1.7)	1
Chest pain	4 (10)	2 (3.5)	0.395
Vomiting	6 (15)	12 (21.4)	0.596
Nausea	3 (7.5)	3 (5.3)	0.999
Loss of appetite	3 (7.5)	2 (3.5)	0.646
Abdominal pain	4 (10)	17 (30.3)	0.023
Altered sensorium	2 (5)	21 (37.5)	< 0.001
Mean arterial pressure (mmHg)*	88.27 ± 24.41	78.62 ± 22.77	0.049
Vasopressor requirement			
Yes	13 (32.5)	26 (46.4)	0.247
No	27 (67.5)	30 (53.5)	
Severity			
Mild[a]	21 (52.5)	21 (37.5)	
Moderate[b]	15 (37.5)	23 (41.07)	0.212
Severe[c]	4 (10)	12 (21.4)	
Ventilation requirement			
Yes	33 (82.5)	53 (94.6)	0.087
No	7 (17.5)	3 (5.3)	

*Data represent mean ± SD; [a]Mild: PaO_2/FiO_2 (PF) ratio 201-300 mm Hg; [b]Moderate: PF ratio 101-200 mm Hg; [c]Severe: PF ratio ≤ 100 mm Hg, based on the lowest PF ratio available on the day of ARDS diagnosis.

Among biochemical variables, hemoglobin, hematocrit, platelet count and serum albumin were significantly lower while serum creatinine, total bilirubin, alkaline phosphatase (ALP), and D-dimer were significantly higher among non-survivors than survivors (p < 0.05 each). Initial SOFA score and APACHE score were significantly higher among non-survivors compared to survivors. The associations between severity illness score such as SOFA score (p = 0.004) and APACHE score (p = 0.002) and outcome were found to be statistically significant (Table 3).

Discussion

In our study, 43.7% of patients were the above age of 60 years. In many studies, advanced age or age above 60 years is an independent predictor of mortality.1, 21 In a study done by Rashid et al.,22 the mean age of recovered patients was significantly lower than the mean age of patients who died (44.41± 14.53 years vs 49.08 ± 16.57 years). In a study of an elderly population of age more than 65 years, Sehgal et al.23 observed that mortality was lower in the elderly population, while we observed that no significant difference existed between the mean age of survivors and non-survivors (57.50 ± 13.72 years vs. 54.66 ± 14.91 years).

In our study, out of 96 patients, 62.5% were males and 37.5% were females. We observed male predominance (male-to-female ratio 1.6:1) that is

similar to other studies with the proportion of males ranging from 56.3% to 60.9%.22-25

Table 3: Laboratory parameters and illness severity scores of survivors and non-survivors

Laboratory parameters	Total patients (n=96)	Survivors (n=40)	Non-survivors (n=56)	p-value
	Median (Range)	Median (Range)	Median (Range)	
Hemoglobin (g/dL)	11.24 (4.8-17.1)	12.65 (7.6-17.1)	10.7 (4.8-17)	0.004
Hematocrit (%)	36.16 (17.28-58.68)	38.09 (19.18-58.68)	34.44 (17.28-55.6)	0.015
White blood cell count (thousand/mm^3)	11.3 (0.3-77.2)	9.9 (2.8-24.3)	12.07 (0.3-77.2)	0.154
Platelet count (lakhs/mm^3)	1.51 (0.003-5.80)	1.77 (3.8-4.14)	1.08 (0.06-5.80)	0.021
Random blood sugar (mg/dL)	139 (38-433)	154 (66-424)	121 (38-433)	0.850
Serum creatinine (mg/dL)	1.51 (0.35-10.52)	1.2 (0.52-10.51)	2.02 (0.35-10.52)	0.047
Serum sodium (mmol/L)	137 (118.7-163.8)	136.7 (118.7-144.9)	137 (119.9-163.8)	0.493
Serum potassium (mmol/L)	4.37 (2.68-8.34)	4.32 (2.71-7.26)	4.41 (2.68-8.34)	0.605
Serum total bilirubin (mg/dL)	0.8 (0.17-13.68)	0.73 (0.17-10.27)	0.94 (0.29-13.68)	0.020
Serum AST (IU/L)	63 (10-5439)	55.5 (15-1353)	74 (10-5439)	0.359
Serum ALT (IU/L)	43 (1-3839)	42 (5-699)	43.5 (1-3839)	0.710
Serum ALP (IU/L)	118.8 (40-1498)	104.5 (40-431)	124.5 (49-1498)	0.011
Serum albumin (g/dL)	2.99 (1.69-5.2)	3.17 (1.97-4.07)	2.65 (1.69-5.2)	< 0.001
Serum LDH (IU/L)	44.15 (179-11045)	416 (179-2103)	522.5 (211-11045)	0.065
D-Dimer (µg/mL)	3.72 (0-10)	2.12 (0-10)	4.51 (0-10)	0.011
Severity illness scores				
SOFA score*				
<8	52 (54.1)	29 (72.5)	23 (41.0)	0.004
>8	44 (45.8)	11 (27.5)	33 (58.9)	
APACHE score*				
<14	35 (36.4)	22 (55)	13 (23.2)	0.002
>14	61 (63.5)	18 (45)	43 (76.7)	

*Data represent number of patients (%); AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; SOFA: sequential organ failure assessment; APACHE: acute physiology and chronic health evaluation.

Many studies suggest that the male gender is more prone to non-recovery or mortality than the female gender among ARDS patients.26 However, we found no significant association between gender and the outcome of patients with ARDS. Our results are in agreement with the results of a study by Rashid et al.22 that no significant association existed between gender and the outcome of patients ($p = 0.074$).

The most common clinical manifestations in our patients were shortness of breath (55.2%), fever (39.5%), altered sensorium (23.9%), and cough (16.6%) while Rashid et al.22 reported that the most common clinical manifestations in patients with ARDS were fever (70.9%), shortness of breath (56.9%) and cough (45%). However, abdominal pain and altered sensorium were found in a higher number of non-survivors than survivors in our study.

Hypertension (32.2%) and type 2 diabetes mellitus (29.1%) were the most common comorbidities seen followed by COPD (15.6%) and CKD (10.4%) among our patients. In another study, the most common comorbidities were hypertension (25.2%), kidney disease (23.8%), and type 2 diabetes mellitus (22.3%), and were significantly associated with mortality which signifies that the presence of comorbidities is associated with greater risk of non-recovery among patients with ARDS.22 However, Sehgal et al.,23 Ando et al.,27 and Finney et al.28 found that there was no significant association between comorbidities and outcome which was consistent with our results of no significant association between comorbidities and outcome of patients with ARDS.

We observed that mean arterial pressure (MAP) was significantly lower among non-survivors than survivors (78.62 mmHg vs. 88.27 mmHg) and is similar to the observations by Balakrishnan et al.29 that MAP was significantly lower in the non-survivor group than the recovered group (61 mmHg vs. 67 mmHg).

Among our patients, vasopressors were needed in 32.5% of survivors and in 46.4% of non-survivors, but the association between the need for vasopressor support and outcome was statistically not significant. On the contrary, in the studies by Balakrishnan et al.29 and George et al.,30 the need for vasopressors was significantly higher among non-survivors than survivors and was associated with increased mortality. However, in a study done by Sharma et al.,24 vasopressor use was not significantly associated with mortality which is in agreement with our findings.

The majority of our patients had mild ARDS (43.7%) followed by moderate ARDS (39.5%) and severe ARDS (16.6%). In a study done by George et al.,30 the majority of patients had moderate ARDS (54.1%) followed by mild ARDS (39.3%) and severe ARDS (6.5%). In another study by Balakrishnan et al.,29 the majority of patients had severe ARDS (36%) followed by moderate ARDS (33%) and mild ARDS (31%).

The difference in the severity of ARDS in different studies may be due to differences in age and etiology of ARDS as per different geographical locations. George et al.30 observed that all patients with severe ARDS succumbed to illness while patients with moderate ARDS showed 42.5% mortality, and those with mild ARDS showed 16.6% mortality. The mortality was comparatively lower among our patients with severe ARDS (75%) and higher in patients with moderate ARDS (60.5%), and those with mild ARDS (50%). However, the association between severity of ARDS and mortality was not significant.

Laboratory parameters such as hemoglobin, platelet count, hematocrit, and serum albumin were significantly lower while serum creatinine, serum total bilirubin, ALP, and D-dimer were higher among non-survivors than survivors among our patients. Our findings are corroborated by findings of a study by Sharma et al.,24 that serum albumin was significantly lower and serum creatinine was significantly higher among non-survivors, while low hematocrit and high serum total bilirubin did not show a significant association with mortality. In the study by George et al.,30 serum creatinine was higher among non-survivors while low serum albumin and raised serum total bilirubin did not have a significant association with mortality. In another study by Sehgal et al.,23 low hemoglobin and low serum albumin levels were

not associated with mortality.

We observed that mechanical ventilation was required for 82.5% of survivors and 94.6% of non-survivors and the difference was statistically not significant. However, Rashid et al.22 found a significant difference between survivors and non-survivors regarding the need for mechanical ventilation which was associated with an increased risk of mortality.

In our patients, the severity of illness scores, such as SOFA and APACHE scores, were higher in the non-survivor group than the survivor group, and the association between the severity of illness scores and the outcome was found to be statistically significant, which is similar to the findings of studies done by Sharma et al.,24 Balakrishnan et al.,29 and George et al.30 that both SOFA and APACHE scores were significantly higher among non-survivors in comparison to survivors.

We noted that overall the most common cause of ARDS was sepsis (45.8%), followed by pneumonia (41.6%). However, in a study done by Sharma et al.,24 the most common cause of ARDS was pneumonia, followed by sepsis. In our patients, the most common cause of direct lung injury was pneumonia, while the most common cause of indirect lung injury was sepsis, which is similar to the findings of the study by George et al.30

The majority of our patients had a non-pulmonary cause of ARDS (55.2%), which is similar to the observations made by Balakrishnan et al.29 and Bhadade et al.31 that non-pulmonary causes of ARDS accounted for 69% and 75% of total patients of ARDS, respectively.

In the study done by Balakrishnan et al.,29 all patients with pulmonary ARDS succumbed to the disease, while out of 43 of our patients with pulmonary ARDS, only 32 patients (74.4%) succumbed to the disease. Rashid et al.22 observed that pneumonia and sepsis were significant predictors of mortality, which is similar to our findings that pneumonia and sepsis had a significant association with the outcome of patients with ARDS.

Mortality occurred in 58.3% of our patients with ARDS, which is similar to mortality rates of 56.2% and 52.5% observed by Sharma et al.24 and Rashid et al.22 However, Sehgal et al.23 and George et al.30 found lower mortality rates, which were 35.8% and 36%, respectively, while Balakrishnan et al.29 observed a higher mortality rate of 79% among patients with ARDS. The difference in mortality rates in various studies may be attributed to differences in the age of patients, duration, etiology, and severity of ARDS, and treatment facilities available at various centers.

Limitations of the study

This study has several limitations. As it was conducted at a single tertiary care center, the findings may not be generalizable to the diverse Indian population, where regional differences in healthcare access and disease burden exist. There may be a potential selection bias as inclusion of only patients admitted to a tertiary care hospital excluded those treated at primary or secondary levels. Long-term follow-up was not available, restricting conclusions to in-hospital outcomes. Despite these limitations, the study provides important insights into ARDS in the Indian context and underscores the need for larger multicenter studies with standardized protocols and extended follow-up.

Conclusions

Etiological factors such as pneumonia and sepsis were associated with an increased risk of mortality. Sepsis was overall the most common cause of ARDS while pneumonia was the most common direct cause of ARDS.

Abdominal pain, altered sensorium, and low mean arterial pressure (MAP) were associated with an increased risk of mortality. Anemia, low hematocrit, low platelet count, hypoalbuminemia, raised serum creatinine, hepatic involvement, and raised D-dimer were predictors of mortality in patients with ARDS. High illness severity scores such as APACHE and SOFA scores were associated with poor outcomes in patients with ARDS.

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Ethics committee approval: The study was approved by the Ethics Committee of Swami Rama Himalayan University, Dehradun, India.

Author contributions: RK, RMK, and RC conceptualized the study. ST and RC performed the clinical assessment. All authors analyzed and interpreted the data. ST drafted the manuscript. RK, RMK, and RC revised the manuscript for its intellectual content. All authors have read and approved the final manuscript

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