Section: General Medicine

Original Research Article

A PROSPECTIVE OBSERVATIONAL STUDY ON ASSESSING PREDICTORS OF OUTCOME IN ARDS IN A TERTIARY CARE CENTER

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ABSTRACT

Background: Acute Respiratory Distress Syndrome (ARDS) is a severe, life-threatening condition characterized by acute hypoxemia and bilateral pulmonary infiltrates not explained by cardiac failure. Despite advances in critical care, ARDS continues to be associated with high morbidity and mortality. Reliable, easily measurable biochemical markers that predict disease severity and outcome are essential for early risk stratification and management. Serum albumin reflects capillary permeability, C-reactive protein (CRP) indicates systemic inflammation, and lactate dehydrogenase (LDH) denotes tissue injury. Their role as predictors of outcome in ARDS remains clinically significant. The aim is to evaluate the correlation of serum albumin, CRP, and LDH with severity and mortality in patients with ARDS.

Materials and Methods: This prospective observational study was conducted from September 2016 to September 2018 in the Department of Medicine at a tertiary care hospital. Adult patients (>18 years) fulfilling the Berlin criteria for ARDS were included. Patients with recent inflammatory diseases, malignancy, liver or renal failure, heart failure, pregnancy, or early death (<24 hours) were excluded. Of 104 enrolled patients, 74 completed day-0 and day-7 biochemical follow-up. Serum albumin, CRP, and LDH were measured on admission and on day 7. ARDS severity was graded using Berlin criteria. Statistical analysis was performed using AUROC curves, sensitivity, specificity, and p-values.

Results: Among 74 patients, mortality was 28.4%. Initial (day-0) values of albumin, CRP, and LDH showed no significant association with mortality. However, the trend of biomarker changes over 7 days correlated strongly with both outcome and severity. Rising albumin and falling CRP and LDH were associated with survival ($p<0.001$ for albumin and CRP; $p=0.015$ for LDH). Biomarker gradients showed strong association with worsening Berlin grades ($p<0.001$). Etiology-specific mortality was highest in ARDS of unknown cause (70%) and lowest in tropical infections (3.3%).

Conclusion: Serial changes in serum albumin, CRP, and LDH over 7 days are superior to baseline values in predicting severity and mortality in ARDS. Etiology significantly influences outcomes, with better survival in ARDS of known infectious origin, especially tropical illnesses.

Keywords: ARDS, Serum albumin, C-reactive protein, Lactate dehydrogenase, Berlin criteria.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) poses frequent complications in critically ill patients, and is responsible for a significant amount of mortality, morbidity and healthcare costs.[1] Many conditions, like sepsis and trauma, which escalate the risk for development or the worsening of ARDS are usually associated with fever. Fever again, may, in turn, aggravate the alveolo-capillary inflammation. ARDS is described as progressive hypoxic disorder with lung infiltration on both sides, as observed on chest

X-ray, due to several causes and not resulting from hydrostatic pulmonary edema. Diffuse alveolar damage is the pathognomic feature of ARDS.

The definition of ARDS has undergone many changes since its description. Berlin definition had shown betterment and generalization over other definitions. It has the following ARDS criteria: The term acute lung injury is no longer used, It should be acute., Presence of bilateral opacities, Heart failure need not be ruled out.

Differentiating ARDS from other diseases is essential, but only a few biomarkers are obtainable. Also for treating the patient the forecasting of severity, response to treatment and end result of the disease is essential.[2] Hence, the need for predictors of outcome and severity of ARDS which reflect the pathology of the disease.

The increased alveolo -capillary permeability is inversely proportional to the serum albumin levels. As described by many studies3 low albumin predicts ARDS and edema in patients who are at risk. CRP is a protein produced through the short term stage of inflammation and is stimulated by the release of cytokines. Severity of a disease can be predicted by CRP.

As the disorder involves destruction of the lung tissue, LDH levels are altered. With the help of these biomarkers the disease progression can be altered by providing proper treatment.

Aims: To study the correlation of albumin, CRP and LDH as predictors of outcome in ARDS. Objectives: To study the correlation between albumin, LDH and CRP and the severity of ARDS as per the Berlin score. To study the correlation between albumin, LDH, and CRP, and the mortality in patients with ARDS. To study the outcome of ARDS based on different etiologies.

MATERIALS AND METHODS

This study was a Prospective Observational study, carried out over a period from September 2016 to September 2018, in the "Department of Medicine", in a tertiary care hospital.

Inclusion criteria

Patients above 18 years of age and Patients with evidence of ARDS admitted to medical ICU's. Exclusion criteria: Patients with any of following in last 3 weeks: Inflammatory conditions; IBD, RA, Malignancy, Liver failure, Glomerular diseases, Hemolytic disorders, Pregnancy, Congestive heart failure, Death within 24 hours.

Methodology: Patients having ARDS are included in the study. Patients with aforementioned exclusion criteria are not included. Patients are classified as having ARDS according to Berlin definition. The severity of ARDS is classified according to Berlin criteria. A structured proforma was designed to record the demographic details, significant history of all the subjects enrolled for the study. The usual biochemical variables, albumin, CRP, LDH and respiratory factors like ventilator settings and chest x rays were observed on day zero and day seven. Serum albumin was measured by Bromocresol method. Lactate-pyruvate technique was used to calculate LDH levels. Immunoturbidimetric method was used to analyze CRP levels. The progression of severity of the disease was observed and the changes in the same biochemical values were observed.

Statistical Analysis: Data collection and computation was done using SPSS And MedCalc version 18.5. Area under the receiver operating characteristic curve (AUROC) and associated variables like sensitivity, specificity were used to correlate biochemical markers with severity. p value of less than 0.005 was considered to be statistically significant.

RESULTS

In our study, a total of 104 patients were included. 30 patients were excluded from the study, as 21 patients had expired before the seventh day. And, 9 patients had left the hospital against medical advice. Hence they also are not available for comparison. So the study was conducted with 74 patients whose serum albumin, serum LDH and CRP were followed on day 0 and day 7.

Of the 74 patients included in the study 47% (35 patients) were male and 53% (39 patients) were female. A total of 5 Patients (6%) were present between the ages 18-20, 26 patients (35%) were of the age group between 20-40, 31 patients (41%) were of the age group between 40-60, 12 patients (16%) were above 60 years of age.

In the age group of 18-20 years, there were 2 male and 3 female patients. In the age group 20-40 years, there were 12 male and 14 female patients. In the age group 40-60 years, there were 16 male and 15 female patients. In the age group above 60 years, there were 5 male and 7 female patients.

Of the 74 patients who were taken, 21 patients (28.4%) have died as compared to 53 patients (71.6%) who have survived. The total death among the study group can be considered as 42 among 95 patients (excluding, 9 patients who had left against medical advice). If these statistics are taken into consideration, the mortality will be about 44.2%.

Table 1: Analysis with the biochemical markers

Outcome	CRP mg/dl	Albumin g/dl	LDH U/l	N
Non survival	148.1	3.1	1233	21
Survived	210	2.9	1102	53
Median	171.45	3.02	1151	
Sensitivity	66.7	61.9	28.6	
Specificity	56.6	62.3	90.6	

P value	0.071	0.595	0.501	

Table 2: Changes in Analysis with the biochemical markers

Outcome	CRP mg/dl	Albumin g/dl	LDH U/l	N
Non survival	45.6	0.19	105	21
Survived	86	0.28	1417	53
Sensitivity	90.5	76.2	47.6	
Specificity	73.6	83	86.8	
P value	< 0.001	< 0.001	0.015	

Table 3: Analysis with gradient in biomarkers with the change in Berlin criteria

Outcome	CRP mg/dl	Albumin g/dl	LDH U/l
Sensitivity	85.7	89.8	91.8
Specificity	80.6	88	52
P value	<0.001	<0.001	0.003

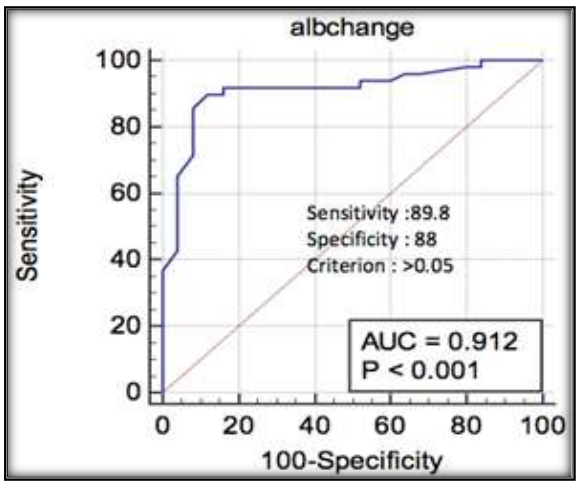

Figure 1: change in albumin vs berlin grade.

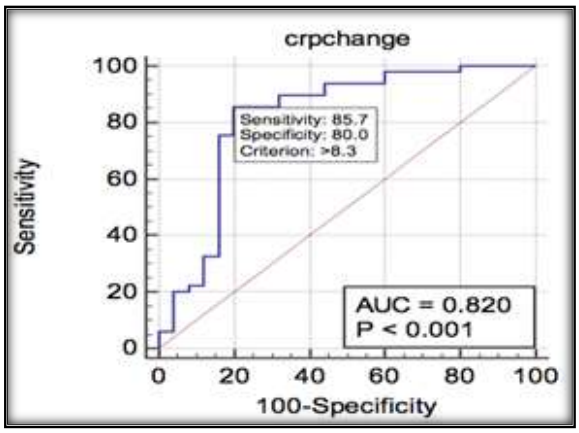

Figure 2: Change In CRP Vs Berlin Grade

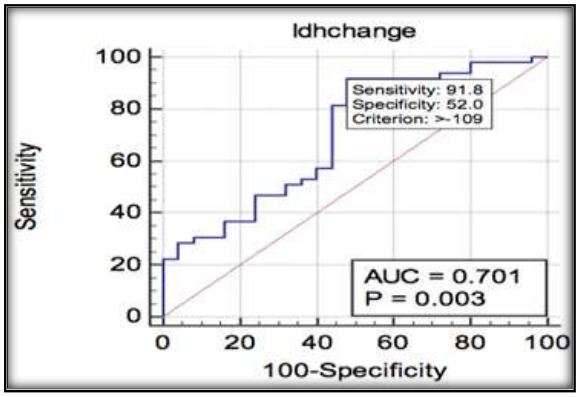

Figure 3: change in LDH vs berlin grade

Of the total number of patients taken (74) , 21 patients were found to have ARDS due to respiratory infections. 30 patients were found to have developed ARDS due to tropical infections (Leptospirosis, Scrub typhus, dengue fever,malaria etc) 3 patients were post operative ARDS. 20 patients had ARDS whose cause was not found.

Of the 21 patients diagnosed with ARDS due to pneumonia, 5 (23.8%) patients have died, while the rest 16 (76.2%) patients survived. Of the 30 patients diagnosed with ARDS due to tropical illnesses. 1 (3.3%) patients has died, while the rest 29 (967%) patients survived.

Of the 3 patients diagnosed with ARDS due to post operative cause 1 (33.3%) patients have died, while the rest 2 (66.7%) patients survived. Of the 20 patients diagnosed with ARDS due to unknown cause, 14 (70%) patients have died, while the rest 6 (30%) patients survived.

DISCUSSION

The present study is a prospective observational study done in a tertiary care hospital to evaluate the significance of albumin, CRP and LDH with the severity and outcome of ARDS and the various etiologies associated with it.

Total 104 patients were included in the study. These are the patients diagnosed as ARDS according to Berlin criteria. In these patients, day 0 and day 7 albumin, CRP and LDH were observed. The progression of the disease and the changes in the biochemical values were observed.

Lower serum albumin levels on the day of diagnosis was associated with poor outcome, i.e., death. However, this value was not found to be very significant according to our study. (p=0.595).

Usually, a lower value of serum albumin should be associated with a poor outcome.

In our study the median values of serum albumin in survivors was observed to be 2.9 g/dl,

Whereas the median values of serum albumin in non-survivors was 3.1 g/dl. This might be due to the fact that we have not taken into consideration the other co-morbidities of the patients into account. Also, there were different etiologies causing the ARDS,

which might have caused this discrepancy in the serum albumin values.

However, a serial raise of serum albumin over a period of 7 days of 0.1 g/dl was associated with good outcome and in all the patients who either had a decrease in serial albumin or an increase which is not more than at least 0.1 g/dl were associated with a poor outcome. ($p<0.001$, sensitivity of 76.2% and specificity of 83%).

Hoeber et al,[4] did a study to evaluate the values of serum albumin, CRP and serum LDH in estimating and predicting ARDS. Serial monitoring of the biochemical markers was done. They concluded that serum albumin is better predictor than CRP and LDH in predicting and grading ARDS.

In a study conducted by Aman J et al,[5] plasma albumin was measured in patients with or at risk for acute lung injury or ARDS before and after fluid load. They concluded that low levels of serum albumin had a high sensitivity of 78-93% and a negative predictive value of about 80-98% for ARDS. The values being 19 □5 mg/l and 17□5 mg/l before and after fluid load.

Arif et al,[6] did a study to assess the importance of serum protein levels for discriminating permeability pulmonary edema in ARDS from cardiogenic pulmonary edema. In their study low serum albumin levels was an indicator of ARDS. The area under curve (AUC) for serum albumin was 0.80 ($p<0.05$). The severity of the disease was also influenced by serum albumin levels.

A study was done by Lee JH et al,[7] to establish the relationship of serum albumin with mortality and unfavorable outcomes in community-acquired pneumonia patients. They concluded that serum albumin was related to 28 day mortality in community-acquired pneumonia patients. For values less than 3.3 mg/dl of serum albumin it was significant.

In our study, the initial value of serum LDH (on Day 0) did not show any significant association to the outcome of ARDS. (Median value of serum LDH in survivor group was 1102 and median value of serum LDH in non-survivor group was 1233) ($p=0.501$). Our study is in accordance with other studies done where higher values of serum LDH were associated with a poor prognosis. There are studies where serum LDH levels were used as an interpreter for ARDS. Some have done studies where the patients who are diagnosed with ARDS showed more activity of serum LDH. However, according to our study, when the serial levels of serum LDH were monitored, it helped predicting the outcome. When the serum LDH levels, which were measured after 7 days, increased or have not decreased by an amount of 109 IU/L, the outcome of patient was poor. ($p=0.015$, sensitivity 47.6%, specificity 86.8 %).

Leff JA et al,[8] did a study on serum antioxidants as an interpreter of ARDS in sepsis patients. One among them is serum LDH. They established that there was augmentation of serum LDH activity in patients who consequently established ARDS than who did not develop ARDS. At serum LDH values ≥250 IU, sensitivity was 67%, specificity 78%, positive predictive value was 50% and the negative predictive value was 88%.

Osaka D et al,[9] conducted a study to assess the role of biomarkers in pneumonia which cause ARDS as complication. Serum LDH was also assessed. They concluded that serum LDH value was high in ARDS group ($p<0.05$) serum LDH value being 274□104 in patients complicated with ARDS. However, the change in serum LDH value at each time point was not significant.

In the study done by Hoeber et al,[4] to evaluate the values of serum albumin, CRP and serum LDH in estimating and predicting ARDS .one of their conclusions being that, serum LDH was a predictor of mortality. In our study, the initial value of CRP taken on day 0, did not show any significant association with the outcome. (Median value of CRP in survivor group was 210 mg/l and median value of CRP in non-survivor group was 148.1 mg/l) ($p=0.071$). Rather, the change in CRP was monitored over a week's time, which showed that a decrease in CRP over a week's time had a favorable outcome and in the patients who had increasing levels of CRP and patients who had decreasing levels of not more than 36 mg/l had a poor outcome. ($p<0.001$, sensitivity 90.5 %, specificity 73.6 %).

A study done by Komiya K et al,[10] to establish the relation between CRP and Acute lung injury. After measuring the levels of CRP within one hour of visit its association with mortality was evaluated. They concluded that with increasing CRP levels, the mortality increased. At levels less than 120 mg/dl the survival was better.

A study was done by Lee JH et al,[7] to establish the relationship of CRP with mortality and unfavorable outcomes in community-acquired pneumonia patients. They concluded that albumin was related to 28-day mortality in community-acquired pneumonia patients. For values less than 14.3mg/dl of CRP it was significant.

Bajwa EK et al,[11] did a study to evaluate the levels of CRP in ARDS and its association with the progression and severity of the disease. CRP levels were checked within 48 hours of the disease onset and it's association with mortality and severity of the disease was determined.

Patients who did not survive had considerably less levels of CRP than who survived. Lower organ dysfunction and ventilator free days were high in patients with more CRP. The results of this study is in contrast to all other studies and in our study where lower values of CRP were associated with favorable outcomes. Overall, in our study, serum albumin is found to be of greater value in predicting and monitoring severity and course of ARDS than CRP and serum LDH. This result is similar to that of the study done by Hoeber et al.[12]

Depending on the etiology of the ARDS, the mortality rates also varied. There was highest mortality, when the etiology of ARDS was not

known. Of a total of 20 patients diagnosed as ARDS with an unknown etiology,[13,14] patients have died. This might be due to the lack of a specific targeted therapy in those with an unknown etiology, compared to when etiology is known and the antibiotics administered targeted specific organism.

Mortality rate was also high in pneumonias. Of 21 patients who had Pneumonia, 5 patients have died. This may be due to the late diagnosis of ARDS in patients with pneumonia where the primary insult may mask the ARDS development.

In patients with tropical illness, the mortality rate was very less. In a total of 30 patients diagnosed to have ARDS due to tropical illnesses, only one patient had died. This might be mainly due to targeted therapy and having a drug of choice for the particular illness. Also, detection of ARDS will be easier in them as, respiratory symptoms are not usually A feature of these, development of ARDS in these patients can be diagnosed very early.

CONCLUSION

Our study has shown that the day 0 laboratory values of the biomarkers- serum albumin, serum LDH and CRP had no role in predicting the outcome of the disease with respect to death or survival. However, the trend of change of laboratory values of the biomarkers- serum albumin, serum LDH and CRP over 7 days, had a significant association with the outcome of the disease with respect to death or survival.

The trend of change of laboratory values of the biomarkers- serum albumin, serum LDH and CRP over 7 days, also had a significant association with the change in ARDS severity, when severity is graded according to Berlin criteria. CRP was a better indicator, than serum albumin and serum LDH when outcome is measured as survival or death. And, serum albumin was better indicator then serum LDH and CRP when the outcome is considered as decrease or increase in the severity of ARDS.

Etiology wise, there was better survival among patients in whom the cause of ARDS was known, than in the patients where the cause of ARDS was not known. Tropical illnesses had a better outcome with respect to patient survival compared to patients who developed ARDS due to other causes like Pneumonia or Post operative causes.

The underlying co morbities of the patients were not taken into consideration which might have changed the course of the disease outcome. Treatment modality was not taken into consideration.

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