Association of serum interleukin-6, interleukin-8, and Acute Physiology and Chronic Health Evaluation II score with clinical outcome in patients with acute respiratory distress syndrome

Deme Swaroopa, Kakarla Bhaskar¹, T. Mahathi, Shivakrishna Katkam², Y. Satyanarayana Raju, Naval Chandra, Vijay Kumar Kutala²

Abstract

Background and Aim: Studies on potential biomarkers in experimental models of acute lung injury (ALI) and clinical samples from patients with ALI have provided evidence to the pathophysiology of the mechanisms of lung injury and predictor of clinical outcome. Because of the high mortality and substantial variability in outcomes in patients with acute respiratory distress syndrome (ARDS), identification of biomarkers such as cytokines is important to determine prognosis and guide clinical decision-making.

Materials and Methods: In this study, we have included thirty patients admitted to Intensive Care Unit diagnosed with ARDS, and serum samples were collected on day 1 and 7 and were analyzed for serum interleukin-6 (IL-6) and IL-8 by ELISA method, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring was done on day 1. Results: The mortality in the patients observed with ARDS was 34%. APACHE II score was significantly higher in nonsurvivors as compared to survivors. There were no significant differences in gender and biochemical and hematological parameters among the survivors and nonsurvivors. Serum IL-6 and IL-8 levels on day 1 were significantly higher in all the ARDS patients as compared to healthy controls and these levels were returned to near-normal basal levels on day 7. The serum IL-6 and IL-8 levels measured on day 7 were of survivors. As compared to survivors, the IL-6 and IL-8 levels were significantly higher in nonsurvivors measured on day 1. Spearman’s rank correlation analysis indicated a significant positive correlation of APACHE II with IL-8. By using APACHE II score, IL-6, and IL-8, the receiver operating characteristic curve was plotted and the provided predictable accuracy of mortality (outcome) was 94%. Conclusion: The present study highlighted the importance of measuring the cytokines such as IL-6 and IL-8 in patients with ARDS in predicting the clinical outcome.

Keywords: Acute respiratory distress syndrome, lung injury, Acute Physiology and Chronic Health Evaluation II, cytokines, mortality
Introduction

Acute respiratory distress syndrome (ARDS) was first described in 1967, and represents a common clinical problem in Intensive Care Unit (ICU) patients. The syndrome is associated with a short-term mortality of approximately 45% as well as significant long-term morbidity. The incidence of ARDS from prospective US cohort studies using the American-European Consensus Conference (AECC) definition ranges from 64.2 to 78.9 cases/100,000 person-years, whereas estimates from Northern Europe (17 cases/100,000), Spain (7.2 cases/100,000), and Australia/New Zealand (34 cases/100,000) have shown substantially lower rates. Studies on ARDS from India are mainly focused on ARDS with various tropical infections such as malaria, miliary tuberculosis, and dengue infections. In a study, Vigg et al. have observed that primary pulmonary infection was associated with ARDS in one-third of patients, and 18% of patients who died with ARDS were with multiorgan failure. In addition, they also found that severe sepsis was a significant risk factor for ARDS. The hallmark lesion in ARDS is widespread destruction of the alveolar epithelium and flooding of the alveolar spaces with proteinaceous exudates containing large numbers of neutrophils. Leukocyte migration is directed to a large extent by chemotactic cytokines. The two major classes include the α-chemokines, which recruit polymorphonuclear neutrophils, whereas β-chemokines recruit monocytes and lymphocytes. The α-chemokines include interleukin-8 (IL-8), GRO (melanoma growth stimulating activity), and epithelial cell neutrophil activating factor (ENA-78). The β-chemokines include the monocyte chemotactic peptides-1, 2, 3, 4 and secreted CCLS. The IL-8, GRO, and ENA-78 are detectable in the bronchoalveolar lavage (BAL) of patients at risk for ARDS and during the course of established ARDS, and on a quantitative basis; IL-8 is the most abundant cytokine present in ARDS patients.

The IL-6 is a cytokine that was originally identified as a B-cell growth factor. IL-6 is produced by activated macrophages and stimulates acute-phase responses in the liver. IL-6 production is induced in part by tumor necrosis factor (TNF-α) and IL-1 β, and it has been proposed that IL-6 “integrates” signals produced early in the inflammatory response. It was found that IL-6 concentrations are very high in the BAL of patients at risk for ARDS and that they remain elevated throughout the course of established ARDS. In a study by Miller et al., they found that IL-8 in BAL at the beginning of ARDS was higher in patients who died, and Donnelly et al. found higher levels of serum IL-8 in patients at risk for ARDS who later developed ARDS. Schütte et al. have observed elevated levels of IL-8 and IL-6 in ARDS, severe pneumonia, or both distinguished these entities from cardiogenic pulmonary edema. Meduri et al. found that all measured cytokines remained high during the course of ARDS in patients who died. Patients who progressed to ARDS had significantly greater BAL levels of IL-8 than those patients who failed to develop ARDS. In a study by Takala et al., among 11 patients with acute pancreatitis, acute lung injury (ALI) patients had significantly higher IL-6, IL-8, and phagocyte CD11b expression levels than did non-ALI patients.

Even though many studies were undertaken, till date, no single biomarker has been identified as a predictor for the outcome of ARDS, rather a combination of biomarkers and scoring systems was suggested to predict the outcomes. Biomarkers were extensively studied which includes plasminogen activator inhibitor-1, IL-6, IL-8, von Willebrand factor antigen, and sTNF-R1 protein and showed independent contributions in predicting ARDS-induced death. Among these, we have selected IL-6 and IL-8 based on their mortality prediction. In addition, the data pertaining ARDS, outcomes, and biomarkers are lacking in the Indian context. Hence, the present study was undertaken to investigate the biomarkers of inflammation such as serum IL-6 and IL-8, age, gender, comorbid conditions including Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and their ability to predict the outcomes of ARDS was also studied.

Materials and Methods

Thirty patients fulfilling the criteria of AECC definition of ARDS and according to AECC criteria including acute onset, PaO2/FiO2 of ≤200, and bilateral infiltrates on chest radiograph and admitted in ICU were included in the study.

Patients with an occlusion pressure of ≥18 mmHg or clinical heart failure and age <18 years were excluded from the study. Exclusion criteria were defined as known underlying lung pathology/heart failure and lung contusion/trauma/burns.

The patients’ clinical history was taken and routine blood and urine investigations including complete hemogram, renal function tests, serum electrolytes, liver function tests, urine routine, chest X-ray, arterial blood gas analysis, and electrocardiogram were done in every patient and also repeated depending on clinical profile. APACHE II scoring was done on day 1. Controls participants comprised age- and sex-matched
healthy individuals recruited from patient’s attendant and hospital staff who are free from any active disease. Detailed history was collected from all the patients. This study was approved by the Institutional Ethical Committee (EC/NIMS/1536/2014) of Nizam’s Institute of Medical Sciences, Hyderabad, India. Informed consent was obtained from the family members of the patients.

Blood samples for IL-6 and IL-8 were collected on day one, i.e., within 24 h of enrollment in the study, and the PaO₂/FiO₂ ratio and mode of ventilation were noted. Second serum sample for IL-6 and IL-8 was collected on day 7, considering day 1 as the day of enrollment in the study. Five milliliters of venous blood sample was collected and allowed to clot at room temperature and was centrifuged at 4000 rpm for 10 min, serum was collected, aliquoted, and stored at −20°C until use. All the other investigations as part of etiological workup for ARDS were done as per the treating physician.

**Measurement of serum cytokines**

Serum IL-6 and IL-8 were measured using human ELISA Kit by Boster’s (USA), based on standard sandwich enzyme-linked immunosorbent assay as per the manufacturer’s instructions.

**Statistical analysis**

Patients were followed up for 28 days, and were grouped based on 28-day mortality into survivor and nonsurvivor groups. The data were analyzed for comparing the IL-6 and IL-8 values in the two groups at baseline, on day 7, and the outcomes such as number of days on ventilator, number of days of ICU stay, comparison of IL-6, IL-8, and APACHE II scoring in predicting the outcomes. Wilcoxon test (continuous variable) and Fisher’s exact test (categorical variable) were used to compare between survivors and nonsurvivors. Analysis of variance was used to calculate the significance among the groups followed by Student’s t-test. Spearman rank correlation was used to establish interrelationships between the different variables. For each predictor variable, sensitivity and specificity were calculated using Fisher’s exact test. Receiver operating characteristic curve (ROC) was plotted using 1-specificity on X-axis (false-positive fraction [FPF]) and sensitivity (true-positive fraction [TPF]) on Y-axis for all the predictor variables.

**Results**

The total number of patients enrolled in the study during the period was 30, with an average age of 46.36 years (19–78 years). Among the 30 patients enrolled, 17 patients recovered, 9 patients died, whereas 4 patients left during the treatment. The average age of 17 patients who survived was 43 years, whereas in nonsurvivors, it was higher, i.e., 52.6 years. Out of 17 survivors, 11 were males and 6 were females. On the other hand, out of nine nonsurvivors, five were females and four were males, with gender having no significance on the outcomes. Demographic characteristics of survivors and nonsurvivors at baseline are shown in Table 1.

As shown in Table 1, there was no significant difference among the average PaO₂/FiO₂ ratio of day 1 which was noted among the survivors and nonsurvivors [Table 1], and similarly, there was no significant difference of systolic blood pressure, diastolic blood pressure, and pulse rate [Table 1]. We found no significant differences in biochemical parameters and hematological parameters among the survivors and nonsurvivors [Table 2].

The average Glasgow coma scale (GCS) among the survivors was 14.6 and the GCS in nonsurvivors was 10. Out of thirty patients, 11 patients (36%) had acute kidney injury (AKI), in which four patients (23.5%) among survivors (n = 17) and four (44.4%) patients among nonsurvivors (n = 9) had AKI. The number of

**Table 1: Demographic details of study patients**

| Characteristics | Survivors (n = 17) | Nonsurvivors (n = 9) |
|-----------------|-------------------|---------------------|
| Age (years)     | 43.8±3.91         | 52.6±6.17           |
| Males/females   | 11/6              | 4/5                 |
| SBP (mm Hg)     | 111.2±3.62        | 116.2±4.7           |
| DBP (mm Hg)     | 70.5±2.18         | 66.6±3.3            |
| PR (beats/min)  | 111.1±4.5         | 104.4±3.16          |
| Respiratory rate (breaths/min) | 38.24±1.5 | 39.56±1.5 |
| PaO₂/FiO₂ ratio | 111.2±3.6         | 104.2±3.7           |

All values are expressed as mean±SD. n: Number of patients; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PR: Pulse rate; SD: Standard deviation

**Table 2: Hematological and biochemical parameters in study patients**

| Characteristics | Survivors (n = 17) | Nonsurvivors (n = 9) |
|-----------------|-------------------|---------------------|
| Hemoglobin (g %) | 10.58±0.47        | 10.99±0.54          |
| Total WBC (count/mm³) | 11.02±11.157 | 14.056±2767         |
| Platelet count (lakhs/cumm) | 2.1±0.26       | 2.4±0.39            |
| Urea (mg/dl)    | 51.35±12          | 47.7±7.5            |
| Creatinine (mg/dl) | 1.28±0.27        | 1.23±0.15           |
| Sodium (mEq/L)  | 126.7±2.61       | 130.3±1.97          |
| Potassium (mEq/L) | 3.94±0.16        | 4.34±0.24           |
| SGOT (U/L)      | 56.41±11.23      | 123±64              |
| SGPT (U/L)      | 56.0±8.3         | 128.3±79.5          |
| Total bilirubin (mg/dl) | 1.38±0.23     | 1.478±0.0.49        |
| Albumin (g/dl)  | 3.15±0.14        | 3.41±0.17           |
| Prothrombin time (s) | 15.18±2.62  | 15.44±11.84         |
| APTT (s)        | 37.01±3.9        | 37.88±2.57          |

All values are expressed as mean±SD. n: Number of patients; WBC: White blood cell; APTT: Activated partial thromboplastin time; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamine pyruvate transaminase; SD: Standard deviation
patients with hepatopathy (>3 times elevation of serum glutamic oxaloacetic transaminase and serum glutamate pyruvate transaminase) were four, out of which, two were among survivors (n = 17) and two were among nonsurvivors (n = 9).

In the current study, out of the thirty patients enrolled, three had disseminated intravascular coagulation (10%), two in survivors and one in nonsurvivors groups. Out of the thirty patients, six patients had hypotension, in which four patients died. Among all the patients enrolled (n = 30), two patients had blood culture positive, one had urine culture positive, one patient had tracheal aspirate culture positive, three patients had smear positive for Plasmodium falciparum, four patients had scrub typhus with serology positive (weil felix 1:640 dil), one patient had dengue serology IgG positive, two patients presented with snake bite, one patient presented with alleged rat poison intake, and two patients had pancreatitis. The average total duration of stay was 7.5 days and the average duration of Icu stay was 3.7 days. The average duration of Icu stay among survivors was 4.7 days, and among nonsurvivors, it was 2.5 days. The percentage of patients on ventilator among survivors and nonsurvivors was 11% and 70%, respectively. The percentage of patients on ventilator among survivors and nonsurvivors was 11% and 70%, respectively. The number of days on ventilator for all patients on an average was 1.1 days, while it was higher in nonsurvivors, i.e., 2 days, among survivors it was 0.8 days. The average number of days on noninvasive ventilation among the survivors was 2.5 days, and among nonsurvivors, it was 0.1 days.

The total duration of hospital stay on average was 7.4 days; among survivors, the average duration of hospital stay was 11.2 days and among nonsurvivors, the average hospital stay was 2.5 days. Out of the thirty patients enrolled, twenty patients had moderate ARDS, six had mild ARDS, and four patients presented with severe ARDS. All the patients with mild ARDS survived, whereas 14 patients with moderate ARDS survived, while six patients died. Out of four patients with severe ARDS, three patients died while one patient survived. The mortality in severe ARDS, moderate ARDS, and mild ARDS was 66.6%, 37.5%, and 14%, respectively. Out of the thirty patients, the average APACHE II score was 15.9; in survivors (n = 17), the average score was 11.88 (7–26) and in nonsurvivors (n = 9), the average score was 21.4 (12–30) [Figure 1].

As shown in Table 3, serum IL-6 and IL-8 levels were significantly increased in ARDS patients as compared to healthy controls. Data when segregated into survivors and nonsurvivors, as shown in Table 4, significantly higher levels of both serum IL-6 and IL-8 levels were observed in nonsurvivors as compared to survivors. Both IL-6 and IL-8 levels were significantly lower on day 7 as compared to day 1 [Table 3]. All the day 7 samples were from the survivors’ group who recovered from ARDS by day 7.

**Correlation between Acute Physiology and Chronic Health Evaluation II with interleukin-6 and -8**

Spearman rank correlation was done to assess the association of the APACHE II with serum IL-6 and IL-8 [Figure 2]. Results indicate the positive correlation with increase of IL-8 and with the increase of APACHE II score (r = 0.41, P < 0.03). There was no association of IL-6 with APACHE II score.

| Table 3: Serum interleukin-6 and 8 levels in controls, acute respiratory distress syndrome, and post-treated acute respiratory distress syndrome |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Biomarker       | Controls (n=20) | ARDS (n=30)    | ARDS on day 7 (n=11) |
| Serum IL-6 (pg/ml) | 38 (31-189)     | 76.5 (31-1893)* | 48 (35-254)*      |
| Serum IL-8 (pg/ml) | 51.5 (39-266)   | 129 (30-675)*   | 76 (40-454)*      |

Data given as median (IQR). Wilcoxon tests were used to compare between the groups. *P<0.001, #P<0.01. IL: Interleukin; ARDS: Acute respiratory distress syndrome; IQR: Interquartile range

| Table 4: Serum interleukin-6 and 8 levels in survivors and nonsurvivors |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Biomarker       | Survivors (n=17) | Nonsurvivors (n=9) |
| Serum IL-6 levels (pg/ml) | 71 (35-563)      | 131 (30-1893)*    |
| Serum IL-8 levels (pg/ml)  | 108 (30-531)     | 302 (48-675)*     |

Data given as median (IQR). Wilcoxon tests were used to compare between survivors and nonsurvivors. *P<0.001. IL: Interleukin; IQR: Interquartile range

![Figure 1: Acute Physiology and Chronic Health Evaluation II score in survivors and nonsurvivors. All values are expressed as mean ± standard deviation, *P < 0.01](image-url)
Receiver operating characteristic curve: Prediction of outcome (mortality) using interleukin-6, -8, and Acute Physiology and Chronic Health Evaluation II score

The predicted probability of mortality was assessed by using ROC curve. We have used three predicted variables, APACHE II score, IL-6, and IL-8, and mortality was used as outcome variable. For each predictor variable, sensitivity and specificity were calculated using Fisher’s exact test. ROC was plotted using 1-specificity (FPF) on X-axis and sensitivity (TPF) on Y-axis for all the predictor variables. A profile with area under the curve (AUC), (C) = 0.5 showed no predictable ability whereas (C) = 1 had a perfect predictable ability. As shown in Figure 3, the area under the ROC curve, C = 0.94 indicated a perfect predictive ability of mortality using these three variables.

Discussion

In patients with ARDS, the initial step in mortality reduction is to identify risk factors for poor clinical outcomes. This is an area being extensively studied. For instance, sepsis-induced ARDS has been found to be associated with the increased risk of death as compared with other causes. There are multiple factors working together to determine the final outcomes of ARDS patients, hence it is more clinically useful to develop a prediction model for risk stratification. In this study, the average age of nonsurvivors was higher than survivors, suggesting older patients appear to be at an increased risk for death. This was illustrated by a multicenter cohort study that followed 1113 patients with ARDS for 15 months. The mortality rate increased progressively with age, ranging from 24% among the patients 15-19 years of age to 60% among the patients with 85 years of age or older. The overall mortality rate was 41%. Earlier studies have reported the increased risk of ALI/ARDS in the elderly; however, other studies have not confirmed this association. In the current study, we did not observe any significant difference in the age in survivors and nonsurvivors. The other observational studies of ARDS patients have had variable findings; but in general, the prognosis seems to be related to age, underlying disease, severity of lung damage, and extrapulmonary organ dysfunction. In most epidemiological studies that have used the AECC ALI and ARDS definitions, age, the underlying medical condition, degree of lung damage, extrapulmonary organ dysfunction, and ongoing sepsis are the most commonly reported predictors of mortality, and the outcome is worse with the increasing age.

In the present study, patients with ARDS were associated with increased serum IL-6 and IL-8 on day 1 and these cytokine levels were significantly higher in nonsurvivors. These findings are in agreement with other studies which demonstrated a similar elevation of cytokines in patients who died compared to patients who survived. In a study done by Ware et al., it was opined that the strong association between the plasma IL-8 concentrations and mortality supports the
important role of plasma IL-8 in the pathogenesis of clinical ALI/ARDS. In another study by Schütte et al., circulating IL-6 levels were comparably elevated in patients with ARDS, though no statistically significant difference between survivors and nonsurvivors was observed.

In a study done by Headley et al. at the onset of ARDS, plasma TNF-α, IL-1β, IL-6, and IL-8 levels were significantly higher in nonsurvivors when compared to survivors. In the study by Meduri et al., they demonstrated that the plasma levels of IL-6 and IL-8 remained significantly elevated in those who died and significantly decreased in survivors, and there was a rapid reduction in plasma inflammatory cytokines over time. Similarly, in the present study, serum IL-6 and IL-8 values on day 7 were significantly lower than day 1 values. Interestingly, all the day 7 values were from survivors, thus the lower values were in accordance with the good clinical outcome. Studies have shown the higher levels of IL-8 in the pulmonary edema fluid and BAL fluid of patients with ALI/ARDS and reported them to be associated with the severity of the disease. In patients with ARDS, the baseline levels of IL-8 in plasma were significantly associated with the mortality. In the ARDS network low tidal volume study, baseline levels of IL-8 in the plasma were significantly associated with mortality and were reduced by the protective ventilator strategy. Given these prior studies, the statistically significant association between plasma IL-8 concentrations and mortality in the current study supports the important role of plasma IL-8 in the pathogenesis of clinical ALI/ARDS.

In the present study, APACHE II score was calculated on day 1 of admission. The scores were higher among the nonsurvivors, and difference among survivors and nonsurvivors was statistically significant in predicting mortality. In addition, serum IL-6 and IL-8 levels were positively correlated with the APACHE II score. The increase of IL-8 with the increase of APACHE II score was statistically significant, whereas no statistically significant association of IL-6 with APACHE II score was observed. Similarly, in the study done by Bone et al. the average APACHE II score in ARDS patients was 19.8 ± 1.4, the serum levels of all studied inflammatory mediators (IL-4, IL-6, IL-6r, IL-8, and IL-10) were significantly correlated to APACHE II score. Serum IL-8 exhibited the strongest correlation with APACHE II score.

In the study by Meduri et al., no statistically significant differences were found between the two groups for any analyzed clinical variable, including age, cause of ARDS, lung injury score, APACHE II score, presence of sepsis, shock, multiple organ dysfunction syndrome, and outcome. In this study, nonsurvivors had a higher number of days on ventilator compared to survivors, but less number of days of ICU stay and total duration of stay owing to early deaths. According to the severity of ARDS (AECC definition), a total of 7 patients had ALI with 14% mortality, and 19 patients had ARDS, with 42% mortality. This is comparable to the mortality rates that were previously noted, i.e. 20%-26% in ALI and 37%-43% in ARDS. According to the New Berlin definition, out of the thirty patients enrolled, seven patients had mild ARDS, twenty patients had moderate ARDS, and three patients had severe ARDS on day 1. The mortality in severe ARDS, moderate ARDS, and mild ARDS was 66.6%, 37.5%, and 14%, respectively. This is similar to mortality rates given by ARDS definition taskforce, i.e., 20%-27% in mild ARDS, 32%-41% in moderate, and 45%-52% in severe ARDS. The other parameters studied including age, etiology, and PaO2/FiO2 ratio had no effect on predicting outcome.

Several studies have indicated the prediction of clinical outcomes in patients with ALI/ARDS which has several advantages such as assessing the disease severity, risk assessment, and establishing the prognosis of individual patients. The use of biological markers greatly improved the correctness of the outcome prognosis in ARDS. We found APACHE II and serum IL-6 and IL-8 to be the best outcome predictors as observed by ROC analysis in ARDS (AUC of 0.94). Similar findings have been reported in previous studies both in BAL and in plasma with regard to the ILs. One advantage of plasma markers is that they are routinely determined. Seven plasma biomarkers such as receptor for advanced glycation end product, procollagen peptide III, brain natriuretic peptide, angiopoietin 2, IL-10, TNF-α, IL-6, and IL-8 possessed great diagnostic accuracy (AUC of 0.86) in distinguishing trauma-induced ALI from controls. Ware et al. studied the combination of biomarkers such as IL-8, SP-D, and clinical predictors and showed that this combination is superior to either clinical predictors or biomarkers alone in predicting the mortality in patients with ALI/ARDS. By using these variables, they found an ROC curve (AUC) of 0.82. In a recent study, in vitro microfluidic assays have demonstrated that the leukocyte stiffening induced by IL-1β, IL-8, TNF-α, and IL-10 in the sera of ARDS patients suggested to play a role in the sequestration of leukocytes in the lung capillary beds during early ARDS. In another study, 13 biomarkers of severe pneumonia-induced ARDS were studied, and the correlation of serum bone morphogenetic protein 15, glypican 3, insulin-like growth factor-binding protein 4,
IL-5, IL-22 binding protein, leptin, and orexin B between day 1 and day 7 of ARDS patients with the severity of the disease was found.[33] In the same study, they found alterations in the inflammation-associated proteins such as IGF-I sR, IGF-II, lipopolysaccharide-binding protein, and leukocyte cell-derived chemotaxin 2 in ALI/ARDS and severe pneumonia patients.[33] The plasma levels of Skip-Cullin-F-box ubiquitin E3 ligase complex, hepatocyte growth factor, macrophage migration inhibitory factor, IL-18, chemokine CXCL10 (IP-10), and monokine induced by interferons-γ measured during 1st and 2nd weeks after the disease onset were found to have significant positive linear correlation with the APACHE II score in patients with avian origin influenza A (H7N9) virus-induced ARDS.[34]

The limitations of the present study are small sample size; we could only analyze two biomarkers, i.e., IL-6 and IL-8 on two time points only. IL levels in BAL was not studied and therefore could not compare its value in relation to serum markers for outcome prediction. However, in this study serum levels of IL6 and IL8 appear to be excellent outcome predictors by ROC analysis.

**Conclusion**

The present study highlighted the importance of measuring cytokines such as serum IL-6 and IL-8 in patients with ARDS for predicting the clinical outcome.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Wallen HD, Sumner R, Ho V, Alkana P. Acute respiratory distress syndrome: Epidemiology and management approaches. Clin Epidemiol 2012;4:159-69.

2. Mohan A, Dhungana A. ARDS in tropical infections. The Association of Physicians of India. http://www.aphiao.org/contents_monograph_2015.html:4-1-9.

3. Vigg A, Mantri S, Vigg A, Vigg A. Clinical profile of ARDS. J Assoc Physicians India 2000;51:855-8.

4. Bachofen M, Welzel ER. Structural alterations of lung parenchyma in the adult respiratory distress syndrome. Clin Chest Med 1982;3:35-56.

5. Deshmone SL, Krenlev S, Amini S, Sawaya BE. Monocyte chemoattractant protein-1 (MCP-1): An overview. J Interferon Cytokine Res 2009;29:313-26.

6. Martin TR. Lung cytokines and ARDS. Roger S. Mitchell lecture. Chest 1999;116 1 Suppl. 28-88.

7. Miller PR, Croce MA, Kilgo PD, Scott J, Fabian TC. Acute respiratory distress syndrome in blunt trauma: Identification of independent risk factors. Am Surg 2002;68:845-50.

8. Donnelly SC, Streiter RM, Reid PT, Kunkel SL, Burdick MD, Armstrong I, et al. The association between mortality rates and decreased concentrations of interleukin-10 and interleukin-1 receptor antagonist in the lung fluids of patients with the adult respiratory distress syndrome. Ann Intern Med 1996;125:191-6.

9. Schütte H, Lohmeyer J, Rossean S, Ziegler S, Siebert C, Kielsch H, et al. Bronchoalveolar and systemic cytokine profiles in patients with ARDS, severe pneumonia and cardiogenic pulmonary oedema. Eur Respir J 1996;9:1858-67.

10. Meduri GU, Heulilly S, Kohler G, Stentz F, Tolley E, Unberger R, et al. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. Chest 1995;107:1062-73.

11. Takala J, Jousela I, Tikhomoi O, Kautiainen H, Jaanson SE, Orpana A, et al. A prospective study of inflammation markers in patients at risk of indirect acute lung injury. Shock 2002;17:352-7.

12. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149 3 Pt 1:818-24.

13. Hudson LD, Milberg JA, Anard D, Maund MBL. Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 1995;151 2 Pt 1:293-301.

14. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353:1685-93.

15. Gong MN, Thompson BT, Williams P, Pothier L, Boyce PD, Christiani DC. Clinical predictors of and mortality in acute respiratory distress syndrome. Potential role of red cell transfusion. Crit Care Med 2005;33:1191-8.

16. Gajic O, Protas-Vivar F, Estaban A, Hulanay RD, Amnute A. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. Intensive Care Med 2005;31:922-6.

17. Toha A, Yamazaki M, Mochizuki H, Noguchi T, Tsuda Y, Kawate E, et al. Lower incidence of acute respiratory distress syndrome in community-acquired pneumonia patients aged 85 years or older. Respirology 2010;15:319-25.

18. Hughes CG, Weavind L, Banerjee A, Mercaudo ND, Schilder J, Pandharipande PF. Intraoperative risk factors for acute respiratory distress syndrome in critically ill patients. Anesthesiology 2010;111:464-7.

19. Brun-Buisson C, Minelli C, Bertolini G, Braizi L, Pimientel J, Lewandowski EK, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. Intensive Care Med 2004;30:51-61.

20. Estassoro E, Dubin A, Lauffair E, Canales H, Scienz G, Moseinec M, et al. Incidence, clinical course, and outcome in 217 patients with acute respiratory distress syndrome. Crit Care Med 2002;30:2450-6.

21. Lahr OR, Karlsson M, Thorsteinsson A, Rylander C, Frostell CG. The impact of respiratory variables on mortality in non-ARDS and ARDS patients requiring mechanical ventilation. Intensive Care Med 2000;26:508-17.

22. Gee MH, Gottlieb J, Albertine KH, Kubis JM, Peters SP, Fish JE. Physiology of aging related to outcome in the adult respiratory distress syndrome. J Appl Physiol 1990;69:822-9.

23. Ware LB, Koyama T, Zhao Z, Janz DR, Wickersham N, Bernard GR, et al. Biomarkers of lung epithelial injury and inflammation distinguish severe sepsis patients with acute respiratory distress syndrome. Crit Care Med 2013;17:6253.

24. Healey AS, Tolley E, Meduri GU. Infections and the inflammatory response in acute respiratory distress syndrome. Chest 1997;111:1396-21.

25. Parsons PE, Eisoner MD, Thompson BT, Matthy MA, Anukievecia M, Bernard GR, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med 2005;33:1-6.

26. Bone RC, Mauder R, Slotman G, Burdick MD, Armstrong I, et al. An early test of survival in patients with the adult respiratory distress syndrome. The PaO2/FiO2 ratio and its differential response to conventional therapy. Prostaglandin E1 Study Group. Chest 1989;96:849-51.
27. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: The Berlin Definition. JAMA 2012;307:2526-33.

28. Lee KS, Choi YH, Kim YS, Baik SH, Oh YJ, Sheen SS, et al. Evaluation of bronchoalveolar lavage fluid from ARDS patients with regard to apoptosis. Respir Med 2008;102:464-9.

29. Lin WC, Lin CF, Chen CL, Chen CW, Lin YS. Prediction of outcome in patients with acute respiratory distress syndrome by bronchoalveolar lavage inflammatory mediators. Exp Biol Med (Maywood) 2010;235:57-65.

30. Fremont RD, Koyama T, Calfee CS, Wu W, Dossett LA, Bossert FR, et al. Acute lung injury in patients with traumatic injuries: Utility of a panel of biomarkers for diagnosis and pathogenesis. J Trauma 2010;68:1121-7.

31. Ware LB, Koyama T, Billheimer DD, Wu W, Bernard GR, Thompson BT, et al. Prognostic and pathogenetic value of combining clinical and biochemical indices in patients with acute lung injury. Chest 2010;137:288-96.

32. Preira P, Forel JM, Robert P, Nègre P, Biarnes-Pelicot M, Xeridat F, et al. The leukocyte-stiffening property of plasma in early acute respiratory distress syndrome (ARDS) revealed by a microfluidic single-cell study: The role of cytokines and protection with antibodies. Crit Care 2016;20:8.

33. Chen C, Shi L, Li Y, Wang X, Yang S. Disease-specific dynamic biomarkers selected by integrating inflammatory mediators with clinical informatics in ARDS patients with severe pneumonia. Cell Biol Toxicol 2016;32:169-84.

34. Guo J, Huang F, Liu J, Chen Y, Wang W, Cao B, et al. The serum profile of hypercytokinemia factors identified in H7N9-infected patients can predict fatal outcomes. Sci Rep 2015;5:10942.