Predicting Survival in ARDS

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Acute respiratory distress syndrome (ARDS) is a fulminant clinical disorder of varied etiology, characterized by diffuse lung injury and severe hypoxemia. It is a leading cause of ICU admission and the associated high mortality has sparked a lot of research on etiology, outcome, scoring systems, mortality predictors, biomarkers including inflammatory cytokines and even genomics in ARDS. The previously used AECC (American European Consensus Conference) definition (1994) of ARDS was replaced by the recent Berlin definition (2012) so as to improve its validity and reliability. This would not only standardize patient enrollment into clinical trials but also help implement the results of these trials into clinical practice. Although various studies have shown a reduction in mortality due to ARDS, it has been largely attributed to the general improvement in critical care and the use of lung protection ventilation strategies. Hence focus on the etiology, co-morbidities, risk factors, complications and mortality predictors, is the need of the hour so as to improve survival. ARDS can occur secondary to multiple causes i.e. either due to direct lung involvement (pneumonia, lung contusion etc) or indirect alveolar damage by inflammatory cytokines (sepsis, trauma, burns, pancreatitis etc.). The causes of ARDS in tropical countries are varied with seasonal variation. Acute febrile illnesses (AFI) like malaria, leptospirosis and dengue usually predominate in the monsoons while H1N1 infection and pneumonias typically peak in the colder winter months. However, malaria, dengue and H1N1 have a potential to be perennial.

The etiology of ARDS will vary according to referral centre, type of ICU and the seasonal incidence of prevalent tropical infections. In the present issue of this journal, Bhadade et al outlined the various etiologies of ARDS in a tropical country. Their study (n=116) showed higher prevalence of infectious diseases (58.89%) as a cause of ARDS associated with a mortality of 47%. The most common causes of ARDS were malaria followed by pneumonia and sepsis in 26.7, 19.8 and 17.2 percent respectively. In Vigg A et al’s retrospective study, 98 patients who died of ARDS in a private tertiary care centre were analyzed. The etiologies were primary pulmonary infection, sepsis with multi-organ failure, polytrauma, pancreatitis and recent abdominal surgery in 30.6, 20, 13.3, 11.1 and 11.1 percent respectively. The etiologies differ because Bhadade et al’s study was in a medical ICU of a public hospital whereas the latter study was in a mixed ICU of a large private setup.

The main emphasis of Bhadade’s study was mortality predictors of ARDS in a medical ICU of a tertiary care public hospital. Managing ARDS patients in such a setup is very challenging due to issues such as late referral, late admission of a deserving patient to ICU (due to resource restricted settings), economic issues and logistic issues like compromised doctor-patient and nurse-patient ratio, lack of 24 hour respiratory care technicians for the ventilated patients and lack of specially formulated diets. An overall mortality rate of 57.8% in his study may seem high in comparison with international data. In the ALIEN study of 255 mechanically ventilated patients with ARDS from 13 geographical areas in Spain, the ARDS ICU mortality was 42.7%. Erickson SE et al analyzed recent trends in acute lung injury mortality in a retrospective cohort of 2451 mechanically ventilated patients enrolled in ARDSnet trial between 1996- 2005. The crude mortality declined from 35% in 1996-97 to 26% in 2004- 2005. They attributed this improvement to advancements in critical care along with lower tidal volume ventilation strategy. A meta-analysis of 72 studies in ALI/ARDS patients by Zambon M and Vincent JL showed mortality rates varying between 15-72%. The overall pooled mortality was 43% with 1.1% per year decline in mortality over 1994 to 2006. Rubenfeld GD et al studied incidence and outcomes of acute lung injury (ALI) in 113 mechanically ventilated patients. The crude incidence of ALI was 78.9 per 100000 person years with in-hospital mortality of 38.5%. Seeley E at al reported a hospital mortality of 41% in a bi-variate analysis of 149 patients of ALI/ARDS.

Various mortality predictors of ARDS have been evaluated in different studies. The scoring systems used have ranged from APACHE, SAPS II and SOFA. A two year study by Monchi et al on predictive factors of survival in ARDS found that SAPS-II, the severity of the underlying medical conditions, the oxygenation index

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They used PaO2/FiO2 (Pf) ratio and was associated with increased did not increase the mortality but Ventilator associated pneumonia Acidosis was found in 22.41% cases reach statistically significant values. platelet count and albumin did not acidosis and multi-organ failure. were male sex, acute kidney failure, SAPS II score and Ppeak at baseline were shown as independent predictors of outcome. Sharma et al in their study on mortality predictors in patients with ALI on lung protective ventilation found older age, cirrhosis, high APACHE II and SAPS II scores, raised oxygenation index, decreased PaO2/FiO2, hemodynamic compromise and acidosis to correlate with disease severity and mortality. In Bhadade’s study, the clinically significant predictors of outcome were male sex, acute kidney injury, coagulopathy, hypotension, acidosis and multi-organ failure. Hemoglobin, leukocyte count, platelet count and albumin did not reach statistically significant values. Acidosis was found in 22.41% cases with a very high mortality of 92.3%. Ventilator associated pneumonia did not increase the mortality but was associated with increased duration of mechanical ventilation. They used PaO2/FiO2 (Pf) ratio and lung injury score (LIS) to diagnose and prognosticate ARDS patients. The mean Pf ratio of survivors was 127.6 ± 60.3 (p value < 0.00005). The Pf ratio is outlined as a variable in LIS, AECC and Berlin definition of ARDS to categorize the severity of ARDS. Initially a Pf ratio <300 mm Hg was used to diagnose ALI and a ratio <200 mm Hg was used to define ARDS. However, the revised Berlin definition for ARDS has classified ARDS as mild (200 <PaO2/FiO2 ≤ 300 mm Hg with PEEP or CPAP > 5 cm H2O), moderate (100 <PaO2/FiO2 ≤ 200 mm Hg with PEEP or CPAP > 5 cm H2O) and severe (PaO2/FiO2 ≤ 100 mm Hg with PEEP or CPAP > 5 cm H2O). Seeley E et al had used both the PaO2/FiO2 ratio and oxygenation index (OI) as mortality predictors. The Pf ratio was a significant predictor of death in unadjusted analysis (odds ratio (OR) 1.57 (CI 1.12 to 3.04)) but not in adjusted analysis (OR 1.29 (CI 0.82 to 2.02)). In contrast the OI was a statistically significant predictor of death in both unadjusted analysis (OR 1.89 (CI 1.28 to 2.78)) and in adjusted analysis (OR 1.84 (CI 1.13 to 2.99)). Oxygenation index has not been used in Bhadade’s study.

The current study used lung injury score (LIS) both as a diagnostic criteria as well as a mortality predictor for ARDS. The lung injury score was designed by Murray and colleagues in 1988. It consists of 4 variables i.e. chest x-ray score, hypoxemia score (PaO2/FiO2), PEEP score and respiratory system compliance score. All variables are scored from 0 – 4 and the final value is calculated by dividing the aggregate sum by the number of variables used. A score of >2.5 is suggestive of severe lung injury. The current study is in accordance with this, as patients with LIS > 2.5 had a high mortality (75%) as compared to those with a LIS < 2.5 who had a lower mortality (39.3%) (p value < 0.0001). The mean LIS in expired patients was 2.68 ± 0.59 while in the survivors was 2.23 ± 0.56 (p value < 0.0001).

The LIS (1988) preceded both the AECC definition for ALI/ARDS (1994) and the Berlin definition of ARDS (2012). The role of LIS in the era of Berlin definition of ARDS has been questioned by Kangelaris KN et al. They tested the association of LIS and its 4 variables calculated on day of ARDS diagnosis with the ARDS morbidity and mortality in a large multi-ICU cohort of 550 patients with Berlin defined ARDS. A one point increase in LIS was associated with 58% increase odds of in-hospital death (p = 0.006), 7% decrease in ventilator free days (p = 0.01), a 25% increase in the days of mechanical ventilation in survivors (p = 0.001) and a 16% increase in the number of ICU days (p = 0.02). However, the mean LIS was only 0.2 points higher in expired patients as compared to survivors. The Berlin stages of severity highly correlated with LIS and were also significantly associated with mortality and morbidity. The predictive validity of LIS for mortality was similar to Berlin stages of severity with no additive value of LIS over Berlin definition. These findings suggest that role of LIS in characterizing the severity of lung injury in the recent era of Berlin definition of ARDS may be limited.

The role of biomarkers in ARDS was reported by Rodrigo Cartin-Ceba et al in 2014. Six biomarkers (von Willebrand factor, thrombin–antithrombin III complex, plasminogen activator inhibitor 1, interleukin 8, receptor for advanced glycation end-products, and club cell secretory protein) were studied and none were found useful to predict hospital mortality in ARDS patients. However, elevated day-1 interleukin 8 levels were associated with the development of multiorgan failure after adjustment for clinical characteristics.

Genomics are destined to change the perspective of mortality predictors in ARDS in the future. Early evidence of genomics impacting ARDS outcome was provided by Marshall in 2002. In 96 patients of ARDS, genotyping of angiotensin converting enzyme (ACE) polymorphism was carried out. The frequency of DD genotype for ACE was associated both with ARDS development and increased mortality. Tejera P et al reported the role of genetics in development of ALI/ARDS from direct or indirect lung injury in 1717 patients. They concluded that ARDS may be influenced by different genetic variants depending on the etiology of lung injury. Functional single nucleotide polymorphisms (SNP) in POPDC3 and FAAH genes may be associated with ARDS due to direct and indirect lung injury.
injury respectively. The cytokine perpetuated lung injury in ARDS may be attenuated by favorable genomes. A study on protective effect of IL1RN coding variant in ARDS revealed that IL1RN SNP rs315952c is associated with decreased risk of ARDS in three population groups with heterogenous ARDS risk factors and the associated increased plasma IL1 receptor antagonist response may attenuate the risk to develop ARDS.

What are the limitations in Bhadade et al’s study? They could have also used oxygenation index in invasively ventilated patients which is proved to be a better predictor of mortality in adjusted analysis. Also if funding was available, cytokines could have been studied especially in the subset of ARDS due to tropical infections. Although a total of 46 patients were initially managed with non-invasive ventilation, 14 patients with PF ratio > 200 required subsequent invasive ventilation with a mortality of 28.6%. It would have been prudent to also discuss the risk factors, baseline severity scores and analyze this subset separately.

Rescue therapies available for severe ARDS include prone position ventilation, High frequency oscillatory ventilation (HFOV) and Extracorporeal membrane oxygenation (ECMO). Prone position improves the ventilation-perfusion mismatch, increases alveolar recruitment and reduces alveolar hyperinflation secondary to high PEEP (positive end expiratory pressure) in ARDS patients. In HFOV small tidal volumes are delivered at a high frequency with high mean airway pressures. In a review of two RCT’s and 12 case series, HFOV was found to show promise but lacked mortality benefit. However the OSCILLATE trial was stopped early in view of higher mortality in HFOV group (47%) as compared to control group (35%) [p=0.005]. The CESAR trial was a landmark trial which showed improved survival in ECMO based management protocol. What is the ultimate therapeutic aim of the mortality predictors of ARDS? The higher cut offs’ eg. LIS > 3 or PF ratio < 100 would identify a subset of severe ARDS patients who could be offered such rescue therapies. In a resource restricted setting this would thus help to channelize the available resources for the most deserving!

**References**


