Identifying an Oxygenation Index Threshold for Increased Mortality in Acute Respiratory Failure

A thesis submitted to the University of Arizona College of Medicine - Phoenix in partial fulfillment of the requirements for the Degree of Doctor of Medicine

Brandon Hammond
Class of 2016

Mentors: Heidi Dalton, MD and Brigham Willis, MD

Abstract

Objectives: To examine current oxygenation index (OI) data and outcomes using EMR data to identify a specific OI values associated with outcome.

Methods: Retrospective review of electronic medical record (EMR) data for patients age 1 month - 20 years mechanically ventilated for >24 hours in the PICU. Serial, average and maximum OI values were calculated. Length of mechanical ventilation, hospital stay and outcome were assessed.

Results: OI was calculated on 65 patients from EMR data, of which 6 died (9.2%). The median maximum OI was 10 for all patients, 17 for non-survivors (NS), and 8 for survivors (S), (p=0.14 via Wilcoxon rank-sum test). Odds ratios (OR) indicated 2.1 times increase odds of death (p=.08), 95% confidence interval (0.89–5.03) for each one-percent increase in maximum OI. Average OI OR also revealed 2.1 times increase in odds of death (p=.14), 95% confidence interval (0.77–5.48). ROC analysis indicated a higher discriminate ability for max OI (AUC = 0.68) than average OI (AUC = .58). OI cut points for mortality were established. Mortality was unchanged until max OI >17, for which mortality nearly tripled at a value of 18% versus 6-7% for range 0-17.

Conclusions: Serial assessment of OI values may allow creation of alert values for increased mortality risk and aid in development of clinical decision rules. Consideration for escalation of therapies for respiratory failure such as high frequency ventilation or ECMO at lower levels of OI than historically reported may be warranted. This study also helps to validate prior reports that OI is useful as a severity score for clinical research and outcome prediction.

Table of Contents:

Section .....Page

Introduction 1

Research Materials & Methods 3

Results 5

Discussion 14

Future Directions 16

References 18

Figures & Tables:

Figure 1: Page 6: Box Plots of Maximum OIs in Survivors and Non-survivors

Figure 2: Page 10: Receiver Operator Characteristic (ROC) Analysis of Maximum OI vs Risk of Death

Table 1: Page 8: Median Maximum and Median Average OIs and Outcomes

Table 2: Page 12: Cut Points for Risk of Death

Introduction

Acute respiratory failure is a common cause for admittance into pediatric intensive care units. Acute respiratory distress syndrome (ARDS) is the most severe form of a wide spectrum of pathologic processes designated as acute lung injury (ALI).[1] Despite advanced treatments such as mechanical ventilation, nitric oxide, surfactant delivery and extracorporeal life support (ECMO), mortality remains high in patients whose ALI and ARDS advance to acute hypoxemic respiratory failure (AHRF).[2]

Advances in understanding the pathophysiology of respiratory failure have led to technological improvements in ECMO and other rescue therapy delivery. With these improvements, previously excluded patient groups with comorbidities and underlying complex chronic problems are receiving therapies such as ECMO with increasing frequency.[3] Well-validated prognostic criteria for implementation of high-resource use and rescue therapies such as ECMO are lacking. Respiratory failure severity calculations, which have been suggested for ECMO candidacy, include the alveolar (A)-arterial (a) oxygen gradient (partial pressure alveolar oxygen (PAO_2) – partial pressure arterial oxygen (PaO2), the P/F ratio (partial pressure arterial oxygen (PaO_2)/fraction inspired oxygen (FiO_2%)), and the oxygenation index (OI).[4] OI is calculated using the equation (mean airway pressure (MAP) x fraction inspired oxygen (FiO_2%))/partial pressure arterial oxygen (PaO_2). Currently, there is no universal consensus among pediatric intensivists of specific values for these calculations that indicate or contraindicate placement of a patient on rescue therapy such as ECMO. Recently, the Pediatric Acute Lung Injury Consensus Conference (PALICC) has defined the pediatric acute respiratory distress syndrome (PARDS) and a stratification system for severity, which builds on the Berlin Definition of adult acute respiratory distress syndrome in adults.[5] As part of this definition, OI is recognized as a primary matrix for respiratory disease severity stratification in mechanically ventilated patients.[6] Historically, an OI of greater than 40 or a sustained OI between 30 and 40 has been associated with high mortality and used as criteria for consideration of ECMO in infants and children. However, recent data suggests that mortality risk may significantly increase at lower levels of OI.[7]

Survival of children with respiratory failure also varies across underlying disorders, diagnoses and co-morbid conditions. OI has been linked to both length of mechanical ventilation and mortality.[4,8,9] A previous study of 131 children with respiratory failure found maximum OI to be an independent predictor of mortality, but could not identify a specific OI threshold for risk of death.[4] Another small study of pediatric stem cell transplant recipients with respiratory failure found that an OI >20 was associated with 94% mortality while patients with an OI >25 had 100% mortality. Maximum OI was also associated with outcome.[9] More recently, the PALICC OI-based severity stratification categories of PARDS were assessed and validated to indicate the highest risk of death in the severe category with OI>16.[10]

Our study expands upon previously reported data on increased mortality risk with lower levels of OI than have been historically used for ECMO candidacy.[11] It also supports and provides additional validation of PALICC PARDS OI thresholds for increased risk of death. Additionally, it examines the utility of the electronic medical record (EMR) as an ongoing source of data for providing serial calculations of the OI. Validation of the EMR as a tool for calculating respiratory severity score measurements, such as serial and maximum OIs, and the associated mortality risks would be of great value to clinicians, as EMRs are becoming omnipresent in today's healthcare environment. Identification of specific trigger levels of OI may permit the creation of critical alert algorithms for the escalation of support (whether advanced respiratory or extracorporeal) in the current era, identify patients who meet entry criteria for clinical research and potentially improve care. Accuracy and efficacy of the EMR to provide severity score calculations and reporting may also reduce the personnel resource burden for manual data collection for research studies, which is a major limitation in performance and participation in clinical research in many small centers or in those without a robust research environment.

Research Materials & Methods

We conducted a retrospective, single-center study with data collected from electronic medical records (EMRs) for patients age 1 month to 20 years, who were mechanically ventilated for more than 24 hours in the PICU of Phoenix Children's Hospital from December 2011 through March 2014. The Phoenix Children's Hospital institutional review board (IRB) reviewed and approved the study. Patients with known intra-cardiac shunts or cyanotic heart disease were excluded. PICU caregivers received no detailed information prior to the study implementation and were not aware that the EMR was being used to obtain data. General patient management of progressive respiratory failure in the PICU at PCH focuses on use of pressure-limited ventilation with tidal volumes <6 cc/kg and peak pressures of <30-35 cm H_2O, use of Positive End-Expiratory Pressures of >5 cm H_2O and limitation of inspired oxygen to less than 60% to maintain saturations of >90%. Use of lower oxygen saturations is permitted in severe cases if hemodynamics and tissue oxygen delivery appears adequate. Use of other modalities, such as high frequency ventilation, inhaled nitric oxide, surfactant, and ECMO, was at the clinician's discretion and no formal treatment algorithm was employed. Although 148 patients met study criteria and were included in the initial census, complete data for serial mean airway pressure (MAP), fraction of inspired oxygen (FiO_2), and partial pressure arterial oxygen (PaO_2) were extractable from the EMR (AllScripts, Inc, Chicago, Il) for only 65 patients (44%). In order to obtain PaO_2 values that were relatively concurrent with MAP and FiO_2 data, measurements were matched within concurrent 4 hour time periods surrounding arterial blood gas analyses. Serial, average and maximum OI were calculated over time for each patient, as well as median average and median maximum OI. The OI is calculated by taking the mean airway pressure in mechanically ventilated patients, the fraction of inspired oxygen and the partial pressure of oxygen in the arterial blood: OI= (mean airway pressure (MAP) x fraction inspired oxygen (FiO_2))/partial pressure arterial oxygen ($P\mathbf{a}O_2$). Length of hospital stay, length of mechanical ventilation, and outcome were also assessed.

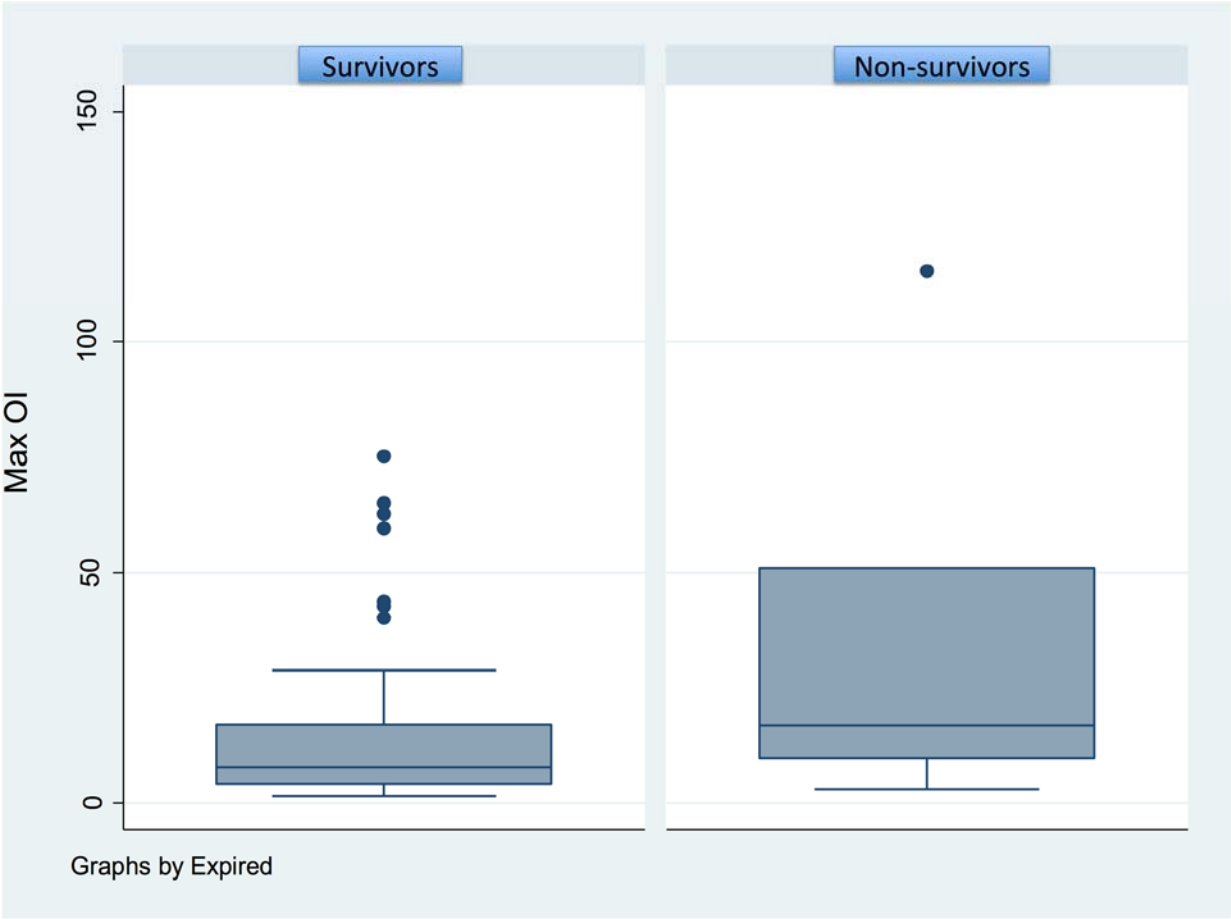
Data were analyzed to characterize and compare the average and maximum OI between the S and NS groups. The data were not normally distributed and therefore presented as the median and interquartile range. Comparisons of continuous data employed the non-parametric

Wilcoxon rank-sum test. Receiver operating characteristic (ROC) analysis was used to assess the discriminant ability of average and maximum OI for survival. To estimate the association between average and maximum OI with the likelihood of survival, the data were log transformed and analyzed with logistic regression. The odds ratio (OR) and 95% confidence intervals (95% CI) are presented. The odds ratio will measure the likelihood of non-survival for one-percent increments in maximum OI and average OI. Statistical significance was defined as an alpha of 0.05, with two-sided alternative hypotheses. Analyses were conducted using Stata 13 (Statacorp, College Station, TX).

Results

Serial OIs were calculated on 65 patients from EMR data. Within this group, 59 patients (91%) survived hospitalization and were discharged, while 6 expired (9%). Maximum OIs from each patient were collected, summed and averaged for all patients. The mean maximum OI for all patients was 17. Mean maximum OI of non-survivors (NS) was significantly higher at 35 versus 15 for survivors (S). However, distributions of maximum and average OIs were found to be non-normally distributed. Median maximum OI values between groups varied considerably. The median maximum OI was 10 or all patients, 17 for NS and 8 for S ($p=0.14$ via Wilcoxon rank-sum). While this does not meet the threshold for statistical significance, difference between groups may be clinically relevant. Interquartile range analysis was used to compare dispersion of data points from median maximum OI in NS and S groups. Interquartile range of maximum OI was 13 for all patients, 12 for S group and significantly wider and more variable at 53 for NS group. Box and Whisker plots for maximum OIs of S versus NS was generated to demonstrate the higher median maximum OI and increased dispersion for NS versus S groups. [Figure 1]

Figure 1: Box Plots of Maximum OIs in Survivors and Non-survivors



Box Plots generated utilizing Stata statistical software. Solid horizontal lines bisecting the boxes indicate medians. Boxes represent inter-quartile ranges, or middle 50% of maximum OIs. Outer brackets are whiskers used to capture maximum OIs outside the middle 50%. Dots are outlier maximum OIs.

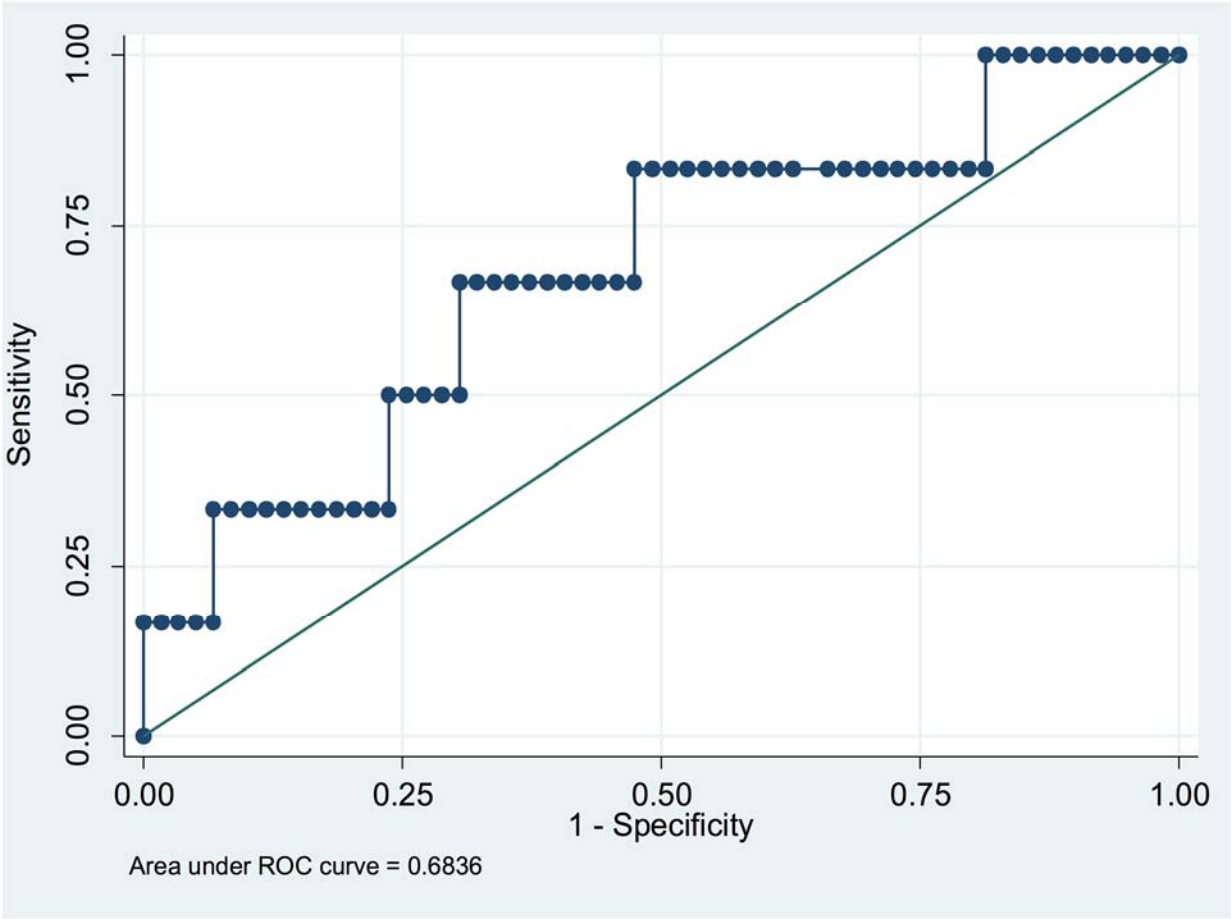
The serial OIs for the duration of mechanical ventilation for each patient were averaged and compared, which again demonstrated non-normal distribution. Median average OI values were closer in proximity for S and NS groups than median maximum OI values, at 4 and 6, respectively (p=.48). [Table 1] The interquartile range for average OI was 7 for all patients, 7 for S, and 20 for NS.

Table 1: Median Maximum & Median Average OIs and Outcomes

Maximum OI	**Survivors (S)**	**Non-survivors (NS)**	**All**
Median	7.57	16.69	9.62
Standard Error	2.21	15.86	2.58
Average OI	**Survivors (S)**	**Non-survivors (NS)**	**All**
Median	4.45	6.19	4.78
Standard Error	0.98	7.81	1.06

Receiver operating characteristic (ROC) curve analysis of maximum and average OI demonstrated an advantage of maximum OI over average OI in discriminatory ability. The area under curve (AUC) for maximum OI was 0.68, while average OI AUC was 0.58. [Figure 2]

Figure 2: Receiver Operator Characteristic (ROC) Analysis of Maximum OI vs Risk of Death



Receiver Operating Characteristic (ROC) curve constructed from maximum OI data points to predict risk of death. The Area Under Curve (AUC) of .68 is indicates fairly accurate discriminatory ability of maximum OI to predict risk of death.

Logistic regression was used to obtain odds ratios for risk of death per one-percent increase in both maximum and average OIs by determining the exponential function of the regression coefficient. After adjusting for age and length of hospitalization, an odds ratio of 2.1 was determined for odds of death with each one-percent increase in maximum OI (p=0.08) over the course of hospitalization, with 95% confidence interval of 0.89 – 5.03. Average OI also resulted in an odds ratio of 2.1, thus increasing the odds of death for each one-percent increase in average OI (p=0.14) over the length of hospitalization, with 95% confidence interval 0.77 – 5.48.

Quartiles were used as guides in establishing cut-points for risk of death. The number of NS and S patients within each quartile were counted. [Table 2] Analysis within each quartile indicated that mortality was unchanged (6-7%) until maximum OI >17. With OI >17, mortality tripled to 18%.

Table 2: Cut Points for Risk of Death

Max OI Cut Points	**< 4**	**4-10**	**10-17**	**> 17**
Number of Patients	16	17	15	17
Percent of Patients	25%	26%	23%	26%
Mortality	1	1	1	3
Mortality within Category	6%	6%	7%	18%

No statistically significant differences were observed between S and NS groups with regard to age or length of hospital stay (LOS). The median LOS was 18 for all patients, 16 for NS and 18 for S. The overall average patient age was 5.6 ± 6.2 years, and median age of 2.8 years. The average survivor age was 5.6 ± 6.1 years and median of 2.4 years. Non-survivor average age was 9.4 ± 5.5-years and median age of 10.4. Length of mechanical ventilation for patients was measured from first recorded MAP to last recorded MAP. The average length of mechanical ventilation for all patients was 19.5 ± 27 days. The median length of mechanical ventilation for all patients was 8.6 days, 9.2 days for survivors and 5.3 days for non-survivors. No additional comorbidities or underlying causes of acute lung injury were explored in this study, other than to exclude patients with known intra-cardiac shunts or cyanotic heart disease.

Discussion

In this study the death rate at OIs >17 was 18%. Additionally, the maximum OI vs risk of death ROC AUC of .68 indicates fairly accurate discriminatory ability in predicting risk of death, and increased discriminatory ability over Average OI. A logistic regression determined odds ratio revealed 2.1 odds of death with each one-percent increase in maximum OI, thought this was not statistically significant. A death rate of 18% may seem modest, but it should be noted that overall mortality in the PICU at our institution (and generally, in PICUs nationwide) is 2-3%. Thus, this mortality in patients with respiratory failure is substantially higher than baseline mortality rates and represents a high-risk group. Historically, an OI of >40 in infants was noted to be associated with high mortality and was used to identify candidates for rescue therapies such as ECMO. This report validates other recent single center studies and the international PALICC group that lower value OIs may be associated with adverse outcome.[6,7,10] Quantifying the predictive capability of the OI and identifying a threshold value for escalation of therapy will help guide discussion regarding appropriate time of rescue intervention. In addition, use of lower OI's for entry criteria into clinical studies of pediatric respiratory failure may also be warranted.[6,10-13] This threshold OI finding warrants further investigation with larger data sets from multiple centers.

The implementation of the electronic medical record (EMR) offers an opportunity to perform serial, automated calculation of values such as the OI for each mechanically ventilated patient. The inclusion of OI into an EMR data-derived severity score algorithm, that then triggers pre-established therapy escalation alerts, has the potential to improve the timeliness of interventions that may improve outcome. Additionally, utilizing the EMR as a research tool has the capacity to improve participation in clinical research or quality improvement projects while allowing a reduction in personnel who have been required for manual extraction and tracking of variables in the past. With the current healthcare environment focused on limitation of expenses, this added benefit may be especially valuable at sites where the research environment is limited. Efficacy of the EMR to capture data may allow increased participation in multi-center studies of care practices and outcomes, which can answer research questions, identify best practice as well as gaps in patient care.

Review of the patient EMR had limited capability in calculating OI. While unit-based personnel were not aware of study specifics and no attempt was made to remind personnel to record variables needed for the OI into the EMR, only 44% of patients had the necessary data recorded within the specified timeframe to calculate OI. The frequency of the PaO_2 being recorded in the EMR within the four-hour time limit associated with MAP and FiO_2 was the greatest limiting factor in expanding the data set. Of note, as patients with respiratory failure may not have an indwelling arterial line from which a PaO_2 can be determined, the PALICC recommendations for pediatric acute respiratory distress syndrome (PARDS) include an oxygenation saturation index as an indicator of severity. In this equation, the PaO_2 is replaced by the arterial oxygen saturation. This score was not calculated in this study, as this recommendation appeared after the study analysis was completed. To improve data capture rates in the future, PICU personnel worked with EMR programmers to define more specific data entry times and alerts when specific parameters (those involved in calculation of oxygenation index in this case) are met. This investigation highlights the need to involve all levels of medical personnel in defining how EMR data is collected and at which time points. While there is danger in the collection of so many data points as to overwhelm servers and make interpretation difficult, it is equally dangerous to make data collection so limited that important values are missed—thus limiting the value of the EMR in research, development of clinical decision tools, and the improvement of patient care and quality.[14] Additional limitations of our study result from the heterogeneity of our subjects with regard to comorbid conditions and underlying diagnoses, which have the potential to significantly influence survivability in acute respiratory failure.

Future Directions

This threshold OI finding of 17 warrants further investigating with larger data sets from multiple centers. In addition, use of lower OI's for entry criteria into clinical studies of pediatric respiratory failure may also be warranted. [6,10,12,13,15] Ongoing evaluation of other parameters of respiratory failure such as the oxygen saturation index may also be obtained from the EMR. Additionally, medical personnel should be trained in the capabilities of their particular EMR, as they may not be cognizant of all that it may provide.[16,17]

Conclusions

Mortality in ventilated PICU patients with a maximum OI of >17 was elevated in this cohort. Historically, entry criteria for rescue therapies such as ECMO generally included significantly higher OI values. Given the three-fold increase in mortality at a value much lower than previously suggested, this study supports the lower thresholds of OI for defining respiratory disease severity as outlined in the newly established PARDS definition. The ubiquity of the EMR is presenting greater possibilities for ease of data access, reconciliation, and functional presentation. Though retrospective application of this technology has limitations, the potential is there to offer real time support in selecting the best treatment modalities in critically ill patients. EMR serial calculation of the OI can be used to assess and track progression of acute respiratory distress in the PICU. EMR clinical decision tools for escalation of rescue therapies such as ECMO, which includes serial and maximum OI calculation, may improve outcomes.

Literature Sited

[1] Monchi M, Bellenfant F, Cariou A, et al. Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis. *Am J Respir Crit Care Med*. 1998; 158(4):1076-1081.

[2] Pathan N, Ridout DA, Smith E, Goldman AP, Brown KL. Predictors of outcome for children requiring respiratory extra-corporeal life support: implications for inclusion and exclusion criteria. *Intensive Care Med*. 2008; 34(12):2256-2263.

[3] Dalton HJ, Butt WW. Extracorporeal life support: An update of Rogers' Textbook of Pediatric Intensive Care. *Pediatr Crit Care Med*. 2012; 13(4):461-471.

[4] Trachsel D, McCrindle BW, Nakagawa S, Bohn D. Oxygenation index predicts outcome in children with acute hypoxemic respiratory failure. *Am J Respir Crit Care Med*. 2005; 172(2):206-211.

[5] Ferguson N, Fan E, Camporota L, et al. The Berlin definition of ARDS: An expanded rationale, justification, and supplementary material. *Intensive Care Med*. 2012; 38: 1573-1582.

[6] Khemani RG, Smith LS, Zimmerman, JJ, et al. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the pediatric acute lung injury consensus conference. *Pediatr Crit Care Med.* 2015; 16(5) S1-40.

[7] Ghuman A, Newth, C, Khemani, R. The association between the end tidal alveolar dead space fraction and mortality in pediatric acute hypoxemic respiratory failure. *Pediatr Crit Care Med.* 2012; 13(1):11-15.

[8] Karimova A, Brown K, Ridout D, et al. Neonatal extracorporeal membrane oxygenation: practice patterns and predictors of outcome in the UK. *Arch Dis Child Fetal Neonatal Ed*. 2009; 94(2):F129-32.

[9] Rowan CM, Hege KM, Speicher RH, et al. Oxygenation index predicts mortality in pediatric stem cell transplant recipients requiring mechanical ventilation. *Pediatric Transplant*. 2012; 16(6):645-650.

[10] Yehya N, Servaes S, Thomas NJ. Characterizing degree of lung injury in pediatric acute respiratory distress syndrome. *Crit Care Med.* 2015; 43(5): 937-946.

[11] Bastin AJ , Firmin R. Extracorporeal membrane oxygenation for severe acute respiratory failure in adults: NICE guidelines. *Heart.* 2011; 97(20): 1701-3.

[12] Khemani RG, Thomas NJ, Venketachalam V, et al. Comparison of SpO_2 to PaO_2 based markers of lung disease severity for children with acute lung injury. *Crit Care Med.* 2012; 40(4): 1309–16.

[13] Bermudez CA, Rocha RV, et al. Extracorporeal membrane oxygenation as a bridge to lung transplant: midterm outcomes. *Ann Thorac Surg.* 2011; 92(4): 1226–31.

[14] Otieno OG, Toyama H, Asonuma M, et al. Nurses' views on the use, quality and user satisfaction with electronic medical records: questionnaire development. *J Adv Nurs.* 2007; 60(2): 209-19.

[15] Fiser SM, Kron IL, McLendon Long S, et al. Early intervention after severe oxygenation index elevation improves survival following lung transplant. *J Heart Lung Transplant.* 2001; 20(6): 631-6.

[16] Greiver M, Barnsley J, Ariarzadeh B, et al. Using a data entry clerk to improve data quality in primary care electronic medical records: a pilot study. *Inform Prim Care.* 2011; 19(4): 241-50.

[17] Valdes I, Kibbe DC, Tolleson G, et al. Barriers to proliferation of electronic medical records. *Inform Prim Care.* 2004; 12(1): 3-9.