



A biomarker-based stratification tool for pediatric acute respiratory distress syndrome: a new approach to an old problem

Joan Balcells^{1,2}, Oriol Roca^{3,4}

¹Pediatric Critical Care Department, Vall d'Hebron University Hospital, Vall d'Hebron Research Institute, Barcelona, Spain; ²Department of Pediatrics, Universitat Autònoma de Barcelona, Barcelona, Spain; ³Critical Care Department, Vall d'Hebron University Hospital, Vall d'Hebron Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain; ⁴Ciber Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain

Correspondence to: Joan Balcells, MD. Pediatric Critical Care Department, Vall d'Hebron University Hospital, Passeig Vall d'Hebron 119-129, 08035, Barcelona, Spain. Email: jbalcells@vhebron.net.

Provenance: This is an invited Editorial commissioned by the Executive Editor Dr. Zhongheng Zhang (Department of Emergency Medicine, Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China).

Comment on: Yehya N, Wong HR. Adaptation of a Biomarker-Based Sepsis Mortality Risk Stratification Tool for Pediatric Acute Respiratory Distress Syndrome. *Crit Care Med* 2018;46:e9-16.

Received: 18 December 2018; Accepted: 02 January 2019; Published: 11 January 2019.

doi: 10.21037/jeccm.2019.01.01

View this article at: <http://dx.doi.org/10.21037/jeccm.2019.01.01>

Assessing the prognosis of a disease is an essential component of a high-quality healthcare process. In the clinical scenario, prognostic information is relevant to prioritizing patients, to selecting treatment modalities or level of care, and to informing patients and relatives about what is expected to happen. From the ethical standpoint, expected prognosis is a key element in the process of ascertaining the suitability of the treatment options being considered. In the administrative arena, baseline prognosis is used to allocate healthcare resources and to evaluate team or institutional performance and benchmarking. Finally, as it relates to research, it is essential to be able to categorize patients in terms of risk as it relates to a specific outcome in order to be able to describe different subgroups of subjects (epidemiological studies), to be able to compare the effect of specific therapeutic approaches between subjects with the same baseline risk (interventional studies) or to be able to select subpopulations most likely to benefit from an intervention in order to maximize the chance of finding a positive therapeutic effect or in order to reduce the size and complexity of the trial to be carried out (trial design).

The different definitions of the acute respiratory distress syndrome (ARDS) that have been proposed since 1994 have all proposed to stratify patients in terms of disease severity. The American-European Consensus Conference (AECC) definition of ARDS (1) recommended that disease severity

and acute lung injury (ALI) subclassification (ALI *vs.* ARDS) should be established by the degree of hypoxemia estimated by partial pressure of oxygen/fraction of inspired oxygen ($\text{PaO}_2/\text{F}_1\text{O}_2$) ratio measurements regardless the need of mechanical ventilation and, consequently, the level of positive end-expiratory pressure (PEEP). Cutoff values were set at a $\text{PaO}_2/\text{F}_1\text{O}_2 \leq 300$ mmHg for the all including ALI category and at a $\text{PaO}_2/\text{F}_1\text{O}_2 \leq 200$ mmHg for ARDS. More recently, the Berlin Definition (2), defined three mutually exclusive subgroups of ARDS (mild, moderate and severe ARDS) according to the $\text{PaO}_2/\text{F}_1\text{O}_2$ ratio (201 to 300 mmHg, 101 to 200 mmHg, ≤ 100 mmHg respectively) measured with PEEP or continuous positive airway pressure (CPAP) ≥ 5 cmH₂O. Empirical evaluation of the draft definition showed that mortality increased and duration of mechanical ventilation in survivors increased significantly with stages of ARDS from mild to severe. Moreover, compared to the AECC definition, the final Berlin definition had a better predictive validity for mortality (AUROC 0.577; 95% CI, 0.561–0.593 *vs.* 0.536; 95% CI, 0.520–0.553; $P < 0.001$).

It should be noted that AECC or Berlin definitions were not specifically conceived for pediatric patients. The Respiratory Section of the European Society for Pediatric and Neonatal Intensive Care (ESPNIC) evaluated the applicability of the Berlin definition to pediatric

population, showing very limited capacity in terms of prognosis discrimination among ARDS strata (3). However, the predictive validity of the Berlin definition was non-significantly superior to the AECC definition (AUROC 0.6; 95% CI, 0.5–0.7; $P=0.04$ vs. 0.52; 95% CI, 0.42–0.62; $P=0.71$). The more recent and specific approach to ARDS characterization in pediatric patients, the pediatric acute respiratory distress syndrome (pARDS) definition of the consensus conference of experts in pediatric lung injury (PALICC) (4) has approached the issue of severity of disease classification and prognosis assessment in terms of oxygen metrics by the use of either invasive ($\text{PaO}_2/\text{F}_1\text{O}_2$ ratio, oxygenation index) or non-invasive (Hb saturation/ F_1O_2 ratio, oxygen saturation index) oxygenation parameters. The discriminative capacity of the proposed parameters, either evaluated at the time of pARDS diagnosis or the worst value during the first three days after diagnosis, was consistently suboptimal (initial $\text{PaO}_2/\text{F}_1\text{O}_2$ ratio AUROC 0.707; 95% CI, 0.652–0.761); initial oxygenation index AUROC 0.723 (95% CI, 0.668–0.776); worst $\text{PaO}_2/\text{F}_1\text{O}_2$ ratio AUROC 0.715 (95% CI, 0.662–0.769); worst oxygenation index AUROC 0.747 (95% CI, 0.697–0.797).

Although hypoxemia has been recognized as a hallmark of ARDS since its first definition in 1967 (5), and oxygen metrics are an essential component of the different ARDS definitions proposed until present, ARDS patients risk stratification based solely on oxygenation parameters is of limited value. Establishing an accurate prognosis, or more appropriately, a precise grouping of ARDS patients in terms of similar prognosis is a complex issue. As acknowledged in the PALISI Consensus Conference (6), prognosis is affected by oxygenation parameters but also by ventilation indexes (disease severity) in as much as patient-specific factors such as comorbidities. A call was made to consider significant comorbidities (specifically immunodeficiency), oxygenation and ventilation defects and biomarkers in an integrated way to evaluate pARDS prognosis within the first 24 hours of onset.

Recently, Yehya and Wong have published in Critical Care Medicine (7) a novel approach to pARDS risk stratification based on age and three biomarkers. Based on the PALISI Consensus Conference recommendation and the opinion of experts in the field (8), a biomarker-based pARDS mortality risk stratification tool has been derived from a biomarker-based sepsis mortality risk stratification model. In previous investigations, Wong HR and colleagues had designed, tested, updated and redefined a pediatric sepsis biomarker risk model (PERSEVERE)

(9-11). At the beginning of the process 12 biomarkers and gender were considered in the classification and regression tree analysis (CART). At the end of the refining process the PERSEVERE-II model included five biomarkers [C-C chemokine ligand 3 (CCL3), interleukin 8 (IL8), granzyme B (GZMB), heat shock protein 70 kDa 1 B (HSPA1B) and matrix metalloprotease 8 (MMP8)] and admission platelet count. In the present report, Yehya and Wong evaluate in the first term the prognostic accuracy of PERSEVERE and PERSEVERE-II models in a cohort of pediatric ARDS patients (according to Berlin definition). Discriminative ability for mortality proved to be poor for both models (PERSEVERE AUROC 0.61; 95% CI, 0.49–0.73; PERSEVERE-II AUROC 0.76; 95% CI, 0.65–0.86). To improve the model the authors developed a new model (PARDSERVERE) initially considering the variables included in PERSEVERE-II and additional variables considered relevant to pARDS prognosis (age, infectious vs. non-infectious ARDS, presence or absence of immunocompromising condition, initial and 24-hour $\text{PaO}_2/\text{F}_1\text{O}_2$ ratio and oxygenation index). After CART analysis, the final PARDSERVERE model retained CCL3, HSPA1B, IL8 and age. Performance of the new model was good both in the derivation and test cohort (AUROC 0.85; 95% CI, 0.78–0.92) and (AUROC 0.82; 95% CI, 0.62–1, respectively) distinguishing three 28-day mortality risk strata: low risk (0–5.6% mortality), intermediate risk (20% mortality) and high risk ($\geq 33\%$). Interestingly and counter intuitively the model did not include the two variables (immunocompromised status and oxygenation parameters) most consistently associated to outcome in previous studies. The reasons for this discrepancy remain speculative, maybe the altered inflammatory process leading to pARDS outcome is better represented by the biomarkers selected than the immunocompromised status or the degree of hypoxemia. Alternatively, as acknowledged by the authors, deaths of neurologic origin may be over-represented in this study.

The study has several limitations, the first being a single center study. Secondly, CART methodology has a risk of overfitting the model to a given dataset (7), thus testing the model in a bigger and center diverse sample is eagerly desired. In fact, it has only been performed an internal validation and an external validation of the results obtained using an independent cohort is mandatory. In this regard, it should be noted that two of the biomarkers retained in the model (IL 8 and MMP 8) have previously been identified as biomarkers associated with pARDS

outcome (12). On the other hand, CART analysis has been criticized because of inherent instability (13). Small changes in data may alter a tree's appearance because, if a split changes, all split subsequent to the affected node may also change. Moreover, it does not provide a statistical output such as a confidence interval in which to quantify or support the validity of the findings. Finally, the measurement of plasma biomarkers may not reflect the biology in the diseased lung. Nevertheless, measuring biomarkers in bronchoalveolar lavage samples may be difficult in many children with a severely compromised respiratory status. In this regard, the question of the value of incorporating biomarkers more specific to ARDS pathogenies remains open.

In summary, adding biomarkers to clinical predictors may be useful for predicting pARDS mortality and may be useful for stratifying patients in clinical trials. This study opens the possibility of setting a new paradigm for pARDS risk stratification.

Acknowledgements

None.

Footnote

Conflicts of Interest: O Roca has received travel expenses from Fisher & Paykel Healthcare and provides consultancy to Hamilton Medical. The other author has no conflicts of interest to declare.

References

- Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818-24.
- Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526-33.
- De Luca D, Piastra M, Chidini G, et al. The use of the Berlin definition for acute respiratory distress syndrome during infancy and early childhood: multicenter evaluation and expert consensus. *Intensive Care Med* 2013;39:2083-91.
- 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:S23-40.
- Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. *Lancet* 1967;2:319-23.
- Flori H, Dahmer MK, Sapru A, et al. Comorbidities and assessment of severity of pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2015;16:S41-50.
- Yehya N, Wong HR. Adaptation of a Biomarker-Based Sepsis Mortality Risk Stratification Tool for Pediatric Acute Respiratory Distress Syndrome. *Crit Care Med* 2018;46:e9-16.
- Vincent JL, Opal SM, Marshall JC. Ten reasons why we should NOT use severity scores as entry criteria for clinical trials or in our treatment decisions. *Crit Care Med* 2010;38:283-7.
- Wong HR, Cvijanovich NZ, Anas N, et al. Pediatric Sepsis Biomarker Risk Model-II: Redefining the Pediatric Sepsis Biomarker Risk Model With Septic Shock Phenotype. *Crit Care Med* 2016;44:2010-7.
- Wong HR, Salisbury S, Xiao Q, et al. The pediatric sepsis biomarker risk model. *Crit Care* 2012;16:R174.
- Wong HR, Weiss SL, Giuliano JS Jr, et al. Testing the prognostic accuracy of the updated pediatric sepsis biomarker risk model. *PLoS One* 2014;9:e86242.
- Orwoll BE, Sapru A. Biomarkers in Pediatric ARDS: Future Directions. *Front Pediatr* 2016;4:55.
- Kuhn L, Page K, Ward J, et al. The process and utility of classification and regression tree methodology in nursing research. *J Adv Nurs* 2014;70:1276-86.

doi: 10.21037/jeccm.2019.01.01

Cite this article as: Balcells J, Roca O. A biomarker-based stratification tool for pediatric acute respiratory distress syndrome: a new approach to an old problem. *J Emerg Crit Care Med* 2019;3:3.