**Online Supplement for “Mean Airway Pressure as a Predictor of 90-day Mortality in Mechanically Ventilated Patients**

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**METHODS**

**Exploratory Analyses**

Since PaO2/FiO2 (a proxy for oxygenation) is a well-established predictor of clinical outcomes, we explored extensively for potential interactions between Pmean and PaO2/FiO2 on mortality. We first examined for an interaction using a multivariable generalized additive logistic regression model in which we used thin plate regression splines for Pmean, PaO2/FiO2, and a thin plate regression surface for the interaction between Pmean and PaO2/FiO2, controlled for the aforementioned variables [21]. We evaluated significance for the interaction term using a Wald test. We explored for non-linear associations in Pmean and PaO2/FiO2 and mortality by modeling the relationship with splines, fractional polynomials, and restricted cubic splines. Once we established that an interaction between Pmean and PaO2/FiO2 was not present, our final multivariable logistic regression model for mortality included the following variables: Pmean, a restricted cubic spline for PaO2/FiO2 with knots at 5th, 50th, and 95th percentiles, age, sex, APACHE III, PEEP, VT per kg PBW, and ICU site as a categorical variable [22].

**Additional sensitivity analyses**

We additionally evaluated the degree of collinearity of all variables with each airway pressure (Pmean, Pplat, Pdriv) using the variance inflation factor and evaluating if changes in our results occurred with the exclusion of potentially collinear variables from our model. Finally, we evaluated the effect of removing several influential but biologically plausible data points from the model to assess their influence on our results.

 **RESULTS**

**Sensitivity analyses**

Total missing data accounted for 8.8% of the data. Of participants missing at least one data variable, 7.1% participants (n = 102) were missing baseline PaO2/FiO2 and 1.7% participants (n=24) were missing baseline VT. Sensitivity analysis for the effect of missing data was performed using multiple imputation techniques under the assumption that data were missing at random. Our inferences regarding the association between increasing Pmean and increasing mortality were unchanged following multiple imputation of missing PaO2/FiO2 and VT values. There was no statistically significant interaction between participants triggering the ventilator and the association between Pmean and mortality. Finally, we explored the robustness of our findings based on the inclusion of PEEP and VT PBW variables, given concerns for collinearity with Pmean. The variance inflation factor was <3.0 for models including Pmean, PEEP, and VT PBW suggesting there was not significant collinearity between these variables. Our findings of the increased odds of death for increasing Pmean remained robust to the exclusion of PEEP and/or VT PBW.

**e-Figure Legends**

**e-Figure 1: Schematic of airway pressure measurements**

Theoretical representation of pressure-time curves demonstrating mean airway pressure (Pmean, dashed line) with different ventilator modes. Breath 1 shows a volume-control breath with decelerating flow. Breath 2 shows a volume-control breath with decelerating flow with an inspiratory pause incorporated. Plateau pressure (Pplat, dotted line) is the pressure during the inspiratory pause. With the inclusion of the inspiratory pause, mean airway pressure is increased. Breath 3 demonstrates a pressure-controlled breath. Abbreviations: PiP – Peak inspiratory pressure, PEEP – Positive end-expiratory pressure, Pmean – mean airway pressure, Pplat – Plateau pressure, Pdriv – driving pressure.

**e-Figure 2: Flow Diagram of selected participants**

**e-Figure 3: Proportion of 90-day mortality by quintiles of mean airway pressure and PaO2/FiO2.** We further evaluated for an interaction between mean airway pressure and PaO2/FiO2 by visually examining the proportion of mortality in each quintile of both mean airway pressure and PaO2/FiO2 ratio. There is a total of 25 cells, where each cell contains the numerical value for the proportion of death and the size of shading of each cell is filled proportionally to that value.

**e-Figure 4: Fitted odds of mortality as a function of mean airway pressure and PaO2/FiO2.** Results are represented as a two-dimensional surface obtained from a generalized additive logistic regression that modelled mortality as a function of a smoothing spline for mean airway pressure, a smoothing spline for PaO2/FiO2 and a bivariate smoothing spline for the interaction between mean airway pressure and PaO2/FiO2 (see details in Supplemental methods). The color of the two-dimensional surface represents the numerical value of the odds of mortality, with higher odds of mortality represented with progressively redder colors and lower odds of mortality represented with progressively bluer colors. These results demonstrate the independent association of Pmean and PaO2/FiO2 with odds of mortality.

**e-Figure 5: Calibration of Airway Pressure in the overall population.** Calibration is characterized by a plot of observed and predicted probabilities of 90-day mortality. The population is divided into 10 equal sized groups and the predicted risk of mortality for each group is represented by the open circle. The straight line in each circle represent the 95% confidence intervals for predicted probability of mortality. The dashed line indicates perfect calibration. The lowess smoother (blue solid line) overlies the line of perfect calibration indicating this model fits the data well in this population.

**e-Figure 6: ROC curves demonstrating the discriminative characteristics of the inspiratory airway pressures (Pmean, Pplat, and Pdriv).**