Characterization and Validation of a Novel Measure of Septic Shock Severity

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Septic Shock; Sepsis; Vasopressors; Hemodynamic Monitoring

Dear Editor,

In critical care, measures that normalize "dose" to physiological response (e.g., PaO_2/FiO_2 in Acute Respiratory Distress Syndrome) can improve mortality prediction and standardize syndrome definitions [1]. Normalized measures in septic shock - such as blood pressure response to vasopressor dose - are poorly studied, but may improve prognostication and identify patients who benefit from specific treatments. We sought to evaluate the prognostic validity of a novel measure of vasopressor responsiveness in septic shock analogous to PaO_2/FiO_2 – the blood pressure to vasopressor dose ratio.

We conducted a retrospective study to validate blood pressure:vasopressor dose ratios using two cohorts of patients with septic shock within 24-hours of ICU admission: the MIMIC-III [2] (2008–2012) and eICU Collaborative Research databases [3] (2014–2015). We determined mean arterial pressure (MAP) and norepinephrine equivalent doses (NEQ) [4] (modified with vasopressin 0.02–0.05 units/min = norepinephrine 10 mcg/min) to calculate MAP:NEQ ratios (MAP/NEQ) every 15 minutes, and then identified the lowest MAP/NEQ within 24-hours of ICU admission. We compared the prognostic validity for hospital

mortality of MAP/NEQ to NEQ using splines and MAP/NEQ to cardiovascular SOFA (CV-SOFA) and the modified cardiovascular SOFA [5] (mCV-SOFA -includes vasopressors missing from CV-SOFA) scores by generating MAP/NEQ tertiles derived from MIMIC-III data. We used logistic regression models to compare discrimination of hospital mortality using c-statistics with bootstrapping to generate 95% confidence intervals. This study was designated by the Boston University IRB as not Human Subjects Research.

MAP/NEQ (mmHg/mcg/kg/min) ranged 39–8396 and 14–10292 and NEQ (mcg/kg/min) ranged 0.01–1.14 and 0.01–2.75 in MIMIC-III (n=1755) and eICU (n=2564) data, respectively. CV-SOFA ranged 1–4 and mCV-SOFA ranged 2–4 in both cohorts. MAP/NEQ had non-linear relationships with mortality (figure). The tertiles to create MAP/NEQ cutoffs were <136 (3-points), 136–324 (2-points), and 325 (1-point). Mortality rates stratified by MAP/NEQ, CV-SOFA, and mCV-SOFA scores are shown in the figure.

In MIMIC-III data, MAP/NEQ had a higher c-statistic (0.65, 95% CI 0.63–0.67) than CV-SOFA (0.60, 95% CI 0.58–0.62, p<0.001)) and mCV-SOFA (0.61, 95% CI 0.59–0.65, p=0.001). In eICU, MAP/NEQ also had a higher c-statistic (0.68, 95% CI 0.66–0.71) than CV-SOFA (0.60, 95% CI 0.58–0.62, p<0.001) and mCV-SOFA (0.63, 95% CI 0.61–0.65, p<0.001). Using splines, MAP/NEQ had a higher c-statistic (0.71, 95% CI 0.69–0.73) than NEQ alone (0.66, 95% CI 0.64–0.69, p<0.001) in eICU data but not in MIMIC-III data (0.68, 95% CI 0.65–0.70 vs 0.67, 95% CI 0.64–0.70, p=0.10).

We evaluated a novel measure of septic shock severity using the ratio of MAP to vasopressor dose (MAP/NEQ). The MAP/NEQ improved prognostic validity compared to commonly used sepsis severity scores and to vasopressor dose alone. A normalized measure such as MAP/NEQ that characterizes vasopressor responsiveness may have prognostication value and standardize comparisons between patients with different MAP targets. Additionally, similar to PaO_2/FiO_2, MAP/NEQ may identify thresholds at which to initiate additional therapies (i.e. corticosteroids in patients with lower MAP/NEQ values) and improve consensus definitions. Future studies may evaluate how MAP/NEQ compares to measures not included in our models (e.g., lactic acid, SvO_2) and test whether MAP/NEQ predicts responsiveness to therapies.

Acknowledgements

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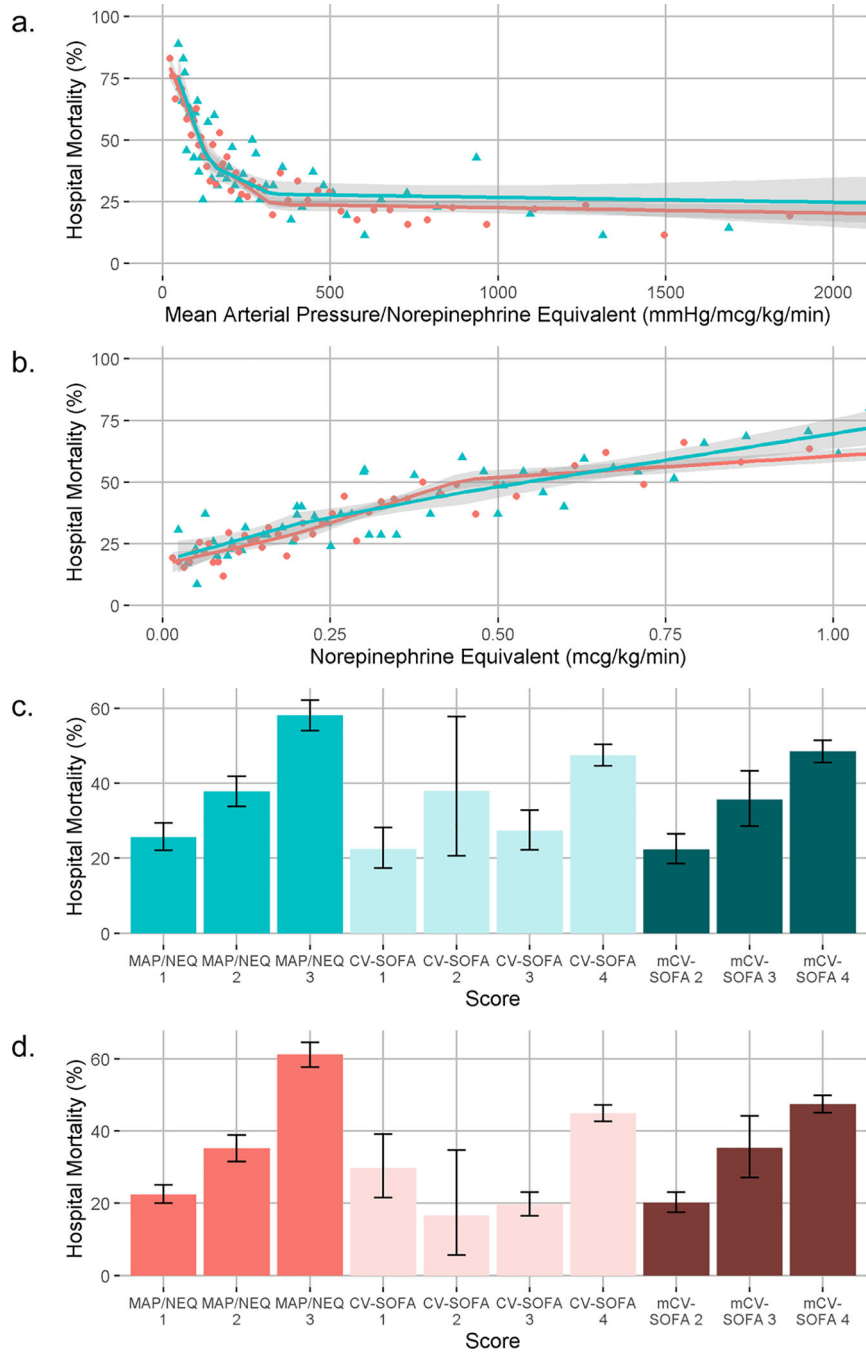
Fig.

a. Relationship between hospital mortality and mean arterial pressure/norepinephrine equivalent dose. Each point represents the percentage of patients who died in the hospital grouped from 50 quantiles of the mean arterial pressure/norepinephrine equivalent dose. Green triangles are from the MIMIC-III cohort, pink circles are from the eICU cohort. Overlying green and pink lines are fitted linear splines (knots at terciles) with 95% confidence intervals. b. Relationship between hospital mortality and norepinephrine equivalent dose. Each point represents the percentage of patients who died in the hospital

grouped from 50 quantiles of the norepinephrine equivalent dose. Green triangles are from the MIMIC-III cohort, pink circles are from the eICU cohort. Overlying green and pink lines are fitted linear splines (knots at terciles) with 95% confidence intervals. c. Stratified mortality of 3-point mean arterial pressure/norepinephrine equivalent dose, cardiovascular sequential organ failure assessment score, and modified cardiovascular sequential organ failure assessment score in the MIMIC-III cohort. Bars show the percent of patients who died and 95% confidence intervals for each score category. d. Stratified mortality of 3-point mean arterial pressure/norepinephrine equivalent dose, cardiovascular sequential organ failure assessment score, and modified cardiovascular sequential organ failure assessment score in the eICU cohort. Bars show the percent of patients who died and 95% confidence intervals for each score category. MAP/NEQ: mean arterial pressure: norepinephrine equivalent dose; CV-SOFA: cardiovascular sequential organ failure assessment; mCV-SOFA: modified cardiovascular sequential organ failure assessment