July 2014 Phoenix Critical Care Journal Club: Predicting the Future

Journal club was held on July 23, 2014 and six articles were reviewed. Four of the articles were on predicting mortality or complications in the ICU. We have long known that older, sicker patients are more likely to die or have complications. However, when attempts are made to go beyond this, it supports one of our favorite Yogisms, "It's tough to make predictions, especially about the future." The last two articles were concerning the best choice for crystalloid administration in adult patients with sepsis and a review article on palliative care in the ICU.

Harhay MO, Wagner J, Ratcliffe SJ, et al. Outcomes and statistical power in adult critical care randomized trials. *Am J Respir Crit Care Med.* 2014;189(12):1469-78. [\[CrossRef\]](#) [\[PubMed\]](#)

Intensive care unit (ICU)-based randomized clinical trials (RCTs) among adult critically ill patients commonly fail to detect treatment benefits. The authors examined 146 RCTs, 54 (37%) were positive (i.e., the a priori hypothesis was found to be statistically significant). The most common primary outcomes were mortality (n = 40 trials), infection-related outcomes (n = 33), and ventilation-related outcomes (n = 30), with positive results found in 10, 58, and 43%, respectively. Statistical power was discussed in 135 RCTs (92%); 92 cited a rationale for their power parameters. Twenty trials failed to achieve at least 95% of their reported target sample size, including 11 that were stopped early due to insufficient accrual/ logistical issues. It was fascinating to see that the *expected* mortality benefit of various investigational treatments in critical care, used to calculate the sample size of each study, was more favorable than the observed mortality benefit in 33 of 34 studies. This probably occurs because overly-optimistic assumptions regarding the possible benefit of the intervention results in lower (more doable) sample size. But when the assumption is found to have been incorrect, as is almost always the case, The study turns out to have been underpowered. The authors conclude that ICU-based RCTs are commonly negative and powered to identify what appear to be unrealistic treatment effects. Additional concerns include a lack of standardized methods for assessing common outcomes, unclear justifications for statistical power calculations, insufficient patient accrual, and incorrect predictions of baseline event rates. As we have repeatedly emphasized in these journal clubs this review supports caution in reading and interpreting clinical trials. A positive result is much easier to obtain with a surrogate outcome such as infection or ventilation parameters but raises the question of the relevance of a surrogate outcome to a patient-centered outcome such as mortality.

Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med.* 2014;189(11):1374-82. [\[CrossRef\]](#) [\[PubMed\]](#)

The authors created a model for predicting hospital survival at initiation of extracorporeal membrane oxygenation (ECMO) for respiratory failure. They used

bootstrapping methodology to examine pre-ECMO variables independently associated with hospital survival on logistic regression, which included age, immunocompromised status, duration of mechanical ventilation before ECMO, diagnosis, central nervous system dysfunction, acute associated nonpulmonary infection, neuromuscular blockade agents or nitric oxide use, bicarbonate infusion, cardiac arrest, PaCO₂, and peak inspiratory pressure to create the Respiratory ECMO Survival Prediction (RESP) score. The receiver operating characteristics curve analysis of the RESP score was $c = 0.74$ (95% confidence interval, 0.72–0.76). External validation, performed on 140 patients, exhibited excellent discrimination ($c = 0.92$; 95% confidence interval, 0.89–0.97). The results are not surprising since these variables have been used to predict survival of ICU patients in general. However, it is reassuring to know that there is nothing unique in predicting survival in patients who receive ECMO.

Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med. 2014;42(6):1340-7. [\[CrossRef\]](#) [\[PubMed\]](#)

Therapeutic hypothermia and pharmacological sedation may influence outcome prediction after cardiac arrest. In this prospective cohort study, the authors used clinical examination, electroencephalography, somatosensory-evoked potentials, and serum neuron-specific enolase, to predict survival in 134 consecutive adults treated with therapeutic hypothermia after cardiac arrest. Multivariable ordinal logistic regression identified absence of electroencephalography reactivity ($p < 0.001$), incomplete recovery of brainstem reflexes in normothermia ($p = 0.013$), and neuron-specific enolase higher than 33 $\mu\text{g/L}$ ($p = 0.029$), but not somatosensory-evoked potentials, as independent predictors of poor outcome. The combination of clinical examination, electroencephalography reactivity, and neuron-specific enolase yielded the best predictive performance (receiving operator characteristic areas: 0.89 for mortality and 0.88 for poor outcome), with 100% positive predictive value.

This study had a fatal methodological flaw – the relationship between survival and the predictor variables was highly biased since the predictor variables were used as criteria for the decision to withdraw care. Most previous studies have demonstrated that neurological examination alone (the lack of withdrawal to pain, or failure to recover cranial nerve reflexes at 72 hours) yielded high positive predictive values for poor outcome. This is the most important statistical characteristic to clinicians when a family asks “what is the chance my father will wake up after this arrest?” Therapeutic hypothermia seems to have pushed back the time frame for prognostication, but hopefully will not create the need for more ancillary testing such as EEGs or serum neuron-specific enolase. The later is a send-out test at our hospital with a long turn-around time. As clinicians retreat from using 32–34° C as a goal for therapeutic hypothermia, based on RCT-evidence that 36° C. is as efficacious, we may be able to retrieve confidence in traditional bedside prognostication that served us well for decades.

The authors caution that although prognostication of poor outcome seems excellent, future studies are needed to further improve prediction of good prognosis, which still remains inaccurate.

Cecchini J, Lionnet F, Djibré M, et al. Outcomes of adult patients with sickle cell disease admitted to the ICU: a case series. Crit Care Med. 2014;42(7):1629-39. [\[CrossRef\]](#) [\[PubMed\]](#)

This was a retrospective observational cohort study of 138 admissions of sickle cell disease patients admitted over a 6-year period to the ICU of a French teaching hospital and sickle cell disease referral center. ICU admissions were mainly indicated for sickle cell disease–related events, especially acute chest syndrome. Those patients with a more complicated outcome group (n = 28; 20%) were characterized by a more aggressive acute disease within the 48 hours preceding ICU admission, with a higher respiratory rate, a more frequent acute kidney injury, and a more sustained drop of hemoglobin (all p < 0.01). In multivariate analysis, hemoglobin less than or equal to 7.8 g/dL (odds ratio, 3.6; 95% CI, 1.1–11.9), respiratory rate more than or equal to 32 cycles/min (odds ratio, 5.6; 95% CI, 1.8–17.2), and acute kidney injury on ICU admission (odds ratio, 11.5; 95% CI, 2.5–52.6) were independently associated with a complicated outcome. Many patients that end up in the ICU with life-threatening complications of sickle cell disease start out as floor admissions with pain crisis. Recognition that those with worse tachypnea, anemia and renal function are at risk to deteriorate could present an opportunity to intensify treatment before sickle chest crisis evolves.

Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med. 2014;42(7):1585-91. [\[CrossRef\]](#) [\[PubMed\]](#)

The authors examined the association between choice of crystalloids and in-hospital mortality during the resuscitation of critically ill adults with sepsis with a retrospective cohort study. They used propensity score matching to control for confounding variables. A total of 53,448 patients at multiple centers with sepsis, treated with vasopressors and crystalloids in an ICU by hospital day 2 were included. Patients treated with balanced fluids were younger and less likely to have heart or chronic renal failure, but they were more likely to receive mechanical ventilation, invasive monitoring, colloids, steroids, and larger crystalloid volumes (median 7 vs 5 L). Among 6,730 patients in a propensity-matched cohort, receipt of balanced fluids was associated with lower in-hospital mortality (19.6% vs 22.8%; relative risk, 0.86; 95% CI, 0.78, 0.94). Mortality was progressively lower among patients receiving larger proportions of balanced fluids. There were no significant differences in the prevalence of acute renal failure (with and without dialysis) or in-hospital and ICU lengths of stay. We usually avoid balanced salt solutions such as Lactated Ringer's because it is sometimes difficult to remember what is actually being administered to the patient. The finding of a lower mortality with balanced salt solutions, if confirmed by a randomized study, is interesting but given the limitations of the study (observational, based on coding, nonrandomized, not confirmed by chart review,

patients receiving balanced salts were less ill, etc.) it was insufficiently persuasive to convince most of us to switch.

Cook D, Rucker G. Dying with dignity in the intensive care unit. N Engl J Med. 2014;370(26):2506-14. [\[CrossRef\]](#) [\[PubMed\]](#)

All of us have cared for patients in the ICU with little to no hope of survival. This review supports the concept that palliative care has come of age in the ICU. At both the VA and Good Samaritan we have been fortunate to have helpful palliative care teams. All of us felt that their input significantly added to care. It was also mentioned that not all patients need to die in an ICU. Palliative care can be valuable in improving death with dignity both in and out of the ICU.

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