Clinical research does not happen in a vacuum. The critical care community has been focused on treating coronavirus disease 2019, the largest global outbreak of respiratory disease in over a century. The pulmonary effects of severe acute respiratory syndrome coronavirus 2 on the lung are frequently manifested as severe ARDS. Knowing which patients are predicted to respond to conventional ARDS management would be a valuable asset to the bedside clinicians facing incredibly difficult therapeutic choices. This trial is a possible first step to that knowledge.

REFERENCES

1. Bower RG, Matthay MA, Morris A, et al; Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New Engl J Med* 2000; 342:1301–1308
2. Gattinoni L, Tognoni G, Pesenti A, et al; Prone-Supine Study Group: Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001; 345:568–573
3. Guerin C, Gaillard S, Lemasson S, et al: Effects of systematic prone positioning in hypoxemic acute respiratory failure: A randomized controlled trial. *JAMA* 2004; 292:2379–2387
4. Taccone P, Pesenti A, Latini R, et al; Prone-Supine II Study Group: Prone positioning in patients with moderate and severe acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2009; 302:1977–1984
5. Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–2168
6. Hu SL, He HL, Pan C, et al: The effect of prone positioning on mortality in patients with acute respiratory distress syndrome: A meta-analysis of randomized controlled trials. *Crit Care* 2014; 18:R109
7. Murray MJ, Cowen J, DeBlock H, et al; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists, American College of Chest Physicians: Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med* 2002; 30:142–156
8. Vender JS, Szokol JW, Murphy GS, et al: Sedation, analgesia, and neuromuscular blockade in sepsis: An evidence-based review. *Crit Care Med* 2004; 32:S554–S561
9. Gainnier M, Roch A, Forel JM, et al: Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. *Crit Care Med* 2004; 32:113–119
10. Papazian L, Forel JM, Gacouin A, et al; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107–1116
11. Fan E, Del Sorbo L, Goligher EC, et al; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine: An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017; 195:1253–1263
12. Schmidt M, Pham T, Arcadipane A, et al: Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome. An international multicenter prospective cohort. *Am J Respir Crit Care Med* 2019; 200:1002–1012
13. Lee HY, Cho J, Kwak N, et al: Improved Oxygenation After Prone Positioning May Be a Predictor of Survival in Patients With Acute Respiratory Distress Syndrome. *Crit Care Med* 2020; 48: 1729–1736
14. Albert RK, Keniston A, Baboi L, et al; Proseva Investigators: Prone position–induced improvement in gas exchange does not predict improved survival in the acute respiratory distress syndrome. *Am J Resp Crit Care* 2014; 189:494–496
15. Lemasson S, Ayzac L, Girard R, et al: Does gas exchange response to prone position predict mortality in hypoxemic acute respiratory failure? *Intensive Care Med* 2006; 32:1987–1993
16. Gattinoni L, Vagginelli F, Carlesso E, et al; Prone-Supine Study Group: Decrease in $PaCO_2$ with prone position is predictive of improved outcome in acute respiratory distress syndrome. *Crit Care Med* 2003; 31:2727–2733
17. Combes A, Hajage D, Capellier G, et al; EOLIA Trial Group, REVA, and ECMONet: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378:1965–1975

Not All Databases Are Created Equal*

Thomas L. Higgins, MD, MBA, MCCM
The Center for Case Management
Natick, MA

It is not quite clear when the threshold was crossed, but we now reside in the age of Artificial Intelligence (AI) in Medicine (AIM). The term "AI" was first used in the 1950s to describe computers that might convincingly mimic the thought processes and behaviors of humans (1). Although it has taken more than 6 decades, data-driven algorithms are now embedded in the electronic health records (EHRs) we employ daily, not to mention in e-commerce, automobiles, smart assistants, social media monitoring, manufacturing, and natural language processing. AIM is increasingly developed using healthcare "big data"; the now voluminous stream of digital information from the EHR, laboratory systems, smartphones, wearable devices, claims-based data, genomic sequencing, research studies, and other sources (2). Insurers, purchasing organizations, governmental agencies, EHR vendors, and others have all assembled large databases; those administrative databases useful for critical care research have been well-summarized elsewhere (3).

Central to the acceptance and adoption of AIM is trust in decision-making algorithms and the data sources that were mined to create those tools (4). The computer science term "Garbage In, Garbage Out," reflects the concept that AI will efficiently process whatever data are provided, but is agnostic to the quality of that data. Inadequate attention to the type and sources of input information will inevitably result in bad (i.e., garbage) output, often in a manner that may be hard to recognize or reconcile. Thus, an emerging frontier of medical research encompasses thoughtful assessment of AIM algorithms,

*See also p. 1737.

Key Words: artificial intelligence; big data; database

Dr. Higgins is a consultant for Cerner Corporation, Kansas City, MO.

DOI: 10.1097/CCM.0000000000004636

challenging their evidence-based assumptions, and investigating the quality of the databases from which they are derived.

The electronic ICU Collaborative Research Database (eICU-CRD) (5) is a publicly available repository with detailed data generated by participants in the Philips Healthcare eICU program. In this issue of *Critical Care Medicine*, O'Halloran et al (6) provide a deep dive into the characteristics of the eICU-CRD. Their descriptive analysis examines data from 139,367 patients admitted to one of 335 participating ICUs between 2014 and 2015. Notably, most encounters were from small and medium-sized hospitals, and patients were managed primarily by nonintensivists with telemedicine backup. Observed ICU mortality was 5.4%, versus an Acute Physiology and Chronic Health Evaluation (APACHE) IVb predicted estimate of 2.0%. In-hospital mortality was 9%. The percentage of patients identified as intubated (15–24%), receiving mechanical ventilation (20–33%), or hemodialysis (3–5%) depended on the query method used. Although most vital sign data fell into realistic ranges, implausible results were occasionally noted. Some of these (temperatures charted in Fahrenheit rather than Celsius) are easily identified; others (such as elevated central venous pressure) may be more elusive. Data entered manually was better curated, a finding that resonates with my own experience. Following an EHR software upgrade, my team spent several months trying to identify suddenly higher ICU standardized mortality ratio (SMR) values. It was our experienced data collector, temporarily reassigned to manually collect parallel data, who finally identified that automated blood pressure values were correctly collected when the nurses chose "ART" (arterial) to label the arterial trace, but not when they chose the alternate "ABP" (arterial blood pressure) label. As a result, missing values in affected patients defaulted to "normal," blood pressure abnormalities were not scored, and thus the falsely low expected mortality translated to an elevated SMR.

Subtle errors can be devilishly difficult to identify, and the process begins with vetting automatically collected data and comparing aggregated median, mean, and SD values to the experience of others. Overall, data from the eICU-CRD was mostly complete and plausible, but relatively low ICU and hospital mortality and length of stay raise the issue of how this database of small and medium-sized facilities compares with larger ICUs with higher patient acuity. While critical care units have been compared using American Hospital Association data (7), specific information on high-acuity units is hard to find. Comparison could be drawn to the Society of Critical Care Medicine's own Project IMPACT database which had a similar number of patients (124,855) at 135 ICUs in 98 hospitals between 2001 and 2004 (8). Project IMPACT was a self-selected consortium of largely urban (49.5%) hospitals where patients were directly managed 51% of the time by critical care specialists, with discretionary or mandatory critical care consultation in 47%. A critical care physician was unavailable only 2% of the time, and ICU telemedicine was then uncommon. Twenty-three percent of the Project IMPACT hospitals had accredited critical care fellowship programs, and an additional 18% were teaching hospitals for a medical school. Only 4% of Project IMPACT units had less than 10 ICU beds, and nearly a quarter had greater than or equal to 20 beds. As might be expected, the Project IMPACT cohort was high acuity, with observed hospital mortality of 13.8%, representing a SMR of 1.018 (0.996–1.040). Other characteristics, although were closer to those observed in the eICU study—for example, 27% of Project IMPACT patients received mechanical ventilation. Unfortunately, detailed comparisons are limited by different definitions, use of mean versus median, and changes in critical care practice over the intervening period.

The APACHE database is another source of descriptive data. Two years' worth of APACHE data, containing 131,618 ICU admissions at 104 ICUs during 2002 and 2003, was used to develop APACHE IV (9). In that model's development set, hospital mortality was 13.6% and 35% of patients were ventilated on ICU day 1. Aggregate median observed ICU length of stay was 1.98 days, longer than the 1.57 days reported by the eICU database.

Differences in patient and ICU characteristics could have important implications when benchmarking mortality and length of stay. Although APACHE and MPM display good overall performance, calibration can diverge from the line of identity at very low or very high scores. Missing data elements (albumin, bilirubin, and pH) will not be scored, and defaulting missing data to normal will predict lower mortality. Furthermore, SMR is usually reported for hospital, not ICU mortality. Thus, it is difficult to say what the high observed to expected mortality ratio in the eICU study might represent. Further study is needed to confirm that existing benchmarking tools accurately predict risk in smaller hospitals where care is provided by nonintensivists with telemedicine backup.

All men are created equal, but all databases are not. Retrospective analyses of large databases collected concurrently with care allows researchers to develop insights that might otherwise be missed due to the prohibitive cost of prospective, randomized controlled studies. But, as the practice of medicine comes to increasingly rely on "big data" for research studies and software development, it is vitally important to fully understand the data sources on which new care algorithms might be based. As the authors acknowledge, caution is warranted in extrapolating findings from the eICU-CRD to larger ICUs with higher acuity. I would contend that the reverse could also be true. This article provides a valuable précis on the strengths and potential weaknesses of one of many available sources of "big data"; our field could use additional similar studies. Understanding the characteristics and limitations of any database is a fiduciary responsibility for researchers to ensure they are not promulgating "fake news."

REFERENCES

1. Amisha, Malik P, Pathania M, Rathaur VK: Overview of artificial intelligence in medicine. *J Family Med Prim Care* 2019; 8:2328–2331
2. NEJM Catalyst: Healthcare Big Data and the Promise of Value-Based Care. 2018. Available at: https://catalyst.nejm.org/doi/full/10.1056/CAT.18.0290. Accessed July 31, 2020
3. Garland A, Gershengorn HB, Marrie RA, et al: A practical, global perspective on using administrative data to conduct intensive care unit research. *Ann Am Thorac Soc* 2015; 12:1373–1386

4. Asan O, Bayrak AE, Choudhury A: Artificial intelligence and human trust in healthcare: Focus on clinicians. *J Med Internet Res* 2020; 22:e15154
5. Pollard TJ, Johnson AEW, Raffa JD, et al: Data descriptor: The eICU collaborative research database, a freely available multi-center database for critical care research. *SciData* 2018; 5:1–13
6. O'Halloran HM, Kwong K, Veldhoen RA, et al: Characterizing the Patients, Hospitals, and Data Quality of the eICU Collaboratove Research Database. *Crit Care Med* 2020; 48:1737–1743
7. Groeger JS, Guntupalli KK, Strosberg M, et al: Descriptive analysis of critical care units in the United States: Patient characteristics and intensive care unit utilization. *Crit Care Med* 1993; 21:279–291
8. Higgins TL, Teres D, Copes WS, et al: Assessing contemporary intensive care unit outcome: An updated Mortality Probability Admission Model (MPM0-III). *Crit Care Med* 2007; 35:827–835
9. Zimmerman JE, Kramer AA, McNair DS, et al: Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006; 34:1297–1310

Another Stepping Stone Toward Personalized Glycemic Control*

Judith Jacobi, PharmD, BCCCP, MCCM
Visante, Inc
Lebanon, IN

The road toward understanding optimal glycemic control in the ICU has been an uneven path. Two decades ago, there was initial enthusiasm for tight glycemic control defined as blood glucose (BG) 4.4–6.1 mmol/L (80–110 mg/dL) based on a trial in surgical ICU patients with remarkable mortality reduction and some morbidity reduction (neuropathy, reduced transfusion, reduced infection, less acute renal failure) in part because the patients were administered concentrated dextrose and control patients who required insulin had mean morning glucose values of 4.1 ± 1.8 mmol/L (insulin therapy target 10–11 mmol/L) (1). Subsequently, many hospitals launched protocols for insulin infusion therapy. Unfortunately, most of these were complex and led to inconsistent frequency of monitoring and excessive hypoglycemia rates, although newer versions have been improved (2). Hypoglycemia was recognized as a significant contributor to poor mortality, especially if severe (< 2.2 mmol/L), odds ratio (OR) 1.87 (95% CI, 1.46–2.4), but even moderate hypoglycemia (3.3–3.9 mmol/L) is a contributor to mortality OR 1.78 (95% CI, 1.39–2.27) (3). The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) multicenter, randomized trial use a computer-assisted protocol and compared insulin infusion to compare a BG goal 4.4–6.1 mmol/L with a more moderate goal of 7.8–11 mmol/L in patients receiving dextrose via enteral rather than IV nutrition (4). This study did not show a benefit of tight glycemic control in this heterogenous population and in fact showed harm, presumably due to an unacceptably high severe hypoglycemic rate of 6.8% with the tight target versus 0.5% with a more liberal target. The adjusted hazard ratio (HR) for increased risk of death was 1.41 (1.21–1.62; $p < 0.001$) for moderate hypoglycemia (2.3–3.9 mmol/L) and 2.10 (1.59–2.7; $p < 0.001$) if severe (< 2.2 mmol/L) (5). In the time since these landmark trials, it has become clear that we have many unresolved questions about glycemic control targets and the role of personalized therapies, but the days of ignoring excessive BG levels or providing an ineffective sliding scale have ended.

However, sites that have used computerized programs to guide insulin dosing and remind the bedside caregivers to monitor BG have been more successful in maintaining glucose within the goal range with lower hypoglycemic rates (2, 6). Guidelines from the Society of Critical Care Medicine (SCCM) and the American Diabetes Association suggest that BG levels be maintained less than 10 mmol/L in critically ill patients, but specific patient populations may benefit from lower BG goals (< 8.3 mmol/L) if it can be done safely (7, 8).

Titrating insulin to a higher BG goal potentially reduces the risk of hypoglycemia. Unfortunately, a gold standard, safe level of hypoglycemia does not exist or even an optimal metric, but clinicians should always seek zero. The Centers for Medicare and Medicaid has proposed a requirement for hypoglycemia monitoring and reporting that has initial endorsement from the National Quality Forum and is open for comments from the public but has not yet been implemented (9).

Data analysis of acute ICU glycemic control is not adequate in isolation, as a link has been established between chronic glycemic control and outcomes with acute therapy. Observational data on critically ill patients suggest a difference in outcome between patients with diabetes mellitus or poor chronic glycemic control, as indicated by glycosylated hemoglobin (HgbA1c) greater than 6.5–7.5 % and the intensity of glycemic control, compared with patients without diabetes—suggesting the need for personalized glycemic control (10). Preliminary data suggest that nondiabetics (labeled as critical illness associated hyperglycemia) may indeed benefit from maintaining BG less than 8.3 mmol/L, whereas diabetic patients with poor chronic glycemic control may be harmed and should be treated with a protocol with a higher goal (11, 12). To test this

***See also p. 1744.**

Key Words: critical care; glycemic control; hyperglycemia; hypoglycemia; insulin

Dr. Jacobi received funding from Society of Critical Care Medicine, AcelRx, Merck, Pfizer, LaJolla Pharmaceuticals, Visante, and WebMD Health Corp/Postgraduate Healthcare Education, and she disclosed off-label product use of insulin for infusion for treatment of hyperglycemia in patients with critical illness associated–hyperglycemia.

DOI: 10.1097/CCM.0000000000004657