Beyond Biomarkers: Machine Learning in Diagnosing Acute Kidney Injury

Bruce A. Molitoris, MD

Nephrology Division Department of Medicine Indiana University School of Medicine, Indianapolis, IN.

Correspondence: Address to Bruce A. Molitoris, MD, Nephrology Division, Department of Medicine, Indiana University, 950 Walnut St, Indianapolis, IN 46202-5114.

Email: bmolitor@iu.edu

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Machine learning is becoming the cutting edge, and likely the way of the future, for patient surveillance. In this issue of Mayo Clinic Proceedings, Chiofolo et al report a Mayo Clinic retrospective, mixed intensive care unit (ICU) study that shows the potential of machine learning with regard to monitoring patients in the ICU environment. Using a continuous random forest analysis technique, the authors first trained and subsequently validated its utility in identifying patients with acute kidney injury (AKI) before an increase in serum creatinine level was detected. Acute kidney injury was defined using standard Acute Kidney Injury Network (AKIN) staging, and known demographic characteristics, hemodynamic variables, ventilation status, fluid details, medications, illness severity, and chronic comorbidities, along with laboratory data, were used for classification. This dynamic model was run every 15 minutes and achieved a remarkable area under the receiver operating characteristic curve of 0.88 in an independent validation cohort, being 92% sensitive and 68% specific for AKIN stages 1 to 3. In 30% of the patients, AKI was detected more than 6 hours in advance of standard classification techniques. In patients with AKI stages 2 and 3, the model had even better sensitivity (91%), specificity (71%), and early detection (53%). So why is this important in the care of ICU patients?

Hospital ICU--acquired AKI remains a common and expensive syndrome associated with a variety of diseases, nephrotoxins, and surgeries, and one that imposes a high rate of morbidity and mortality and an increased length of hospital stay and costs. The early diagnosis of AKI is difficult because it is a clinically silent syndrome, with the diagnosis dependent on laboratory determinations and/ or a decrease in urine output. In addition, without a specific therapy, some even question why surveillance and early diagnosis would be beneficial and therefore necessary. However, a series of studies

reported from different hospital centers around the world beginning in 2002 showed that nonecritically ill patients initially, and critically ill patients subsequently, with AKI evaluated early after diagnosis by nephrology consultation exhibited reduced mortality and need for dialysis and improved renal outcomes.2-5 Whether this resulted from additional attention to hemodynamic parameters, volume status, and avoidance of nephrotoxic agents (such as radiocontrast or nephrotoxic antibiotics) was not determined but was presumed to be the case by many nephrologists. This finding was followed by the development and use of electronic AKI alert systems based on serum creatinine values to provide early recognition across all hospital acute care specialties.6,7 Subsequent use of a clinical decision support system based on early AKI detection revealed a decrease in hospital mortality, dialysis use, and length of stay.8 These studies set off a cascade of events leading to the potentially clinically important use of machine learning approaches so elegantly and persuasively described by Chiofolo et al.1 This study thus introduces a novel methodological approach that may predict AKI earlier than detecting it by serum creatinine elevations and is predicated on the notion that earlier detection would ultimately enhance care and improve outcomes beyond electronic AKI alert approaches based on serum creatinine level.

This first step in reducing the time to the diagnosis of AKI was identification of risk factors associated with its occurrence. A study by Thakar et al9 produced a risk development score for patients undergoing cardiothoracic surgery. Although primarily developed for enrollment of high-risk patients in clinical AKI therapeutic studies, identification of high-risk patients could also be envisioned as the first step toward increasing attention to hemodynamics and monitoring of the results of laboratory tests

and urine output. Accompanying this increasing emphasis on identifying patients at a high risk for AKI was the search for novel urinary and serum biomarkers for the diagnosis of AKI. The use of these AKI biomarkers has a history, consequences, and relevance well beyond the scope of this editorial. Although these various biomarkers exhibit varying sensitivities in detecting AKI and arise from different pathobiologic mechanisms in the acutely injured kidney, they are all united by the common hopedindeed, the common promisedthat such biomarkers would identify AKI before serum creatinine concentration became diagnostic. This factor relates to many challenges when using serum creatinine as the diagnostic tool for AKI, including first the nature of the relationship between serum creatinine and glomerular filtration rate (GFR) and second the existence of renal functional reserve.10 Serum creatinine is so insensitive to a decrease in GFR in patients with normal GFR that in many patients AKI is undetected when quantifying serum creatinine. For instance, many individuals donating a kidney for transplant have less than a 0.3 mg/dL increase in their serum creatinine level (the increment in serum creatinine used by the AKIN to diagnose AKI), even though they have lost one-half of their total kidney function. Therefore, loss of up to 50% of total kidney function in these patients would not have been registered as AKI. Thus, one use for the novel biomarkers is to identify “subclinical AKI” as a serum creatinineenegative but biomarker-positive diagnosis, indicating the presence of renal tubular epithelial cell injury. Patients with subclinical AKI detected by urinary biomarkers alone are known to have a worse outcome than biomarker- and serum creatinineenegative patients.11 Another important use for biomarkers is their predictive value in ruling out the likelihood of development of AKI12; for example, in this latter study, if the cell cycle urinary biomarkers were absent there was

less than a 5% chance that the patient would have development of AKI. However, use of these biomarkers is expensive, and this must be considered before considering routine surveillance protocols.

Therefore, attention has turned to other approaches to identify patients with a high probability of AKI and alert the physician to its likely occurrence. In particular, both electronic health records and noneelectronic health recordebased risk algorithms derived from patient demographic characteristics, medical history, vital signs, and laboratory values offered a dynamic and inexpensive approach to predict AKI before serum creatinine elevations.13,14 Subsequent studies incorporated additional data sources including medications, transfusions, diagnostics, and interventions to predict AKI in advance of serum creatinine diagnostic criteria.15,16 These retrospective studies used machine learning to develop an AKI prediction tool on a training cohort and then applied them to a validation cohort.

The present model differs from previous contributions to this field in several important and positive ways. First, the model was run across time, thereby offering a dynamic approach to patients in the ICU setting. Second, the model was computer-calculated, which thus provided near real-time information for surveillance purposes without physician input or time. Third, it was based on and used in all ICU patients and not subgroups of patients, as many of the previous studies have done.

Although the authors delineated several limitations in their study, the significance of this type of approach will only be proven by a prospective, randomized, double-blind, controlled study comparing outcomes in ICU patients with and without the use of such a

system. This step will of course be dependent on the actions taken by physicians in response to the information supplied. Such a study using e-alerts for AKI defined by serum creatinine level, and not machine learning surveillance as in the present study, found a reported increase in AKI, a reduced length of stay, and improvements in the quality of care but no change in the 30-day AKI mortality rate.17 Perhaps machine learningemediated surveillance, with earlier recognition of AKI, will offer additional improvements in the care of the patient with AKI. The exciting prospect that machine learningemediated surveillance may confer salutary outcomes in AKI and reduce attendant morbidity and mortality should be examined in further studies.

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