Early Prediction of Acute Kidney Injury in the Emergency Department With Machine-Learning Methods Applied to Electronic Health Record Data

Diego A. Martinez, PhD; Scott R. Levin, PhD; Eili Y. Klein, PhD; Chirag R. Parikh, MD, PhD; Steven Menez, MD; Richard A. Taylor, MD, MHS; Jeremiah S. Hinson, MD, PhD*

*Corresponding Author. E-mail: hinson@jhmi.edu, Twitter: @Hinson_EM.

Study objective: Acute kidney injury occurs commonly and is a leading cause of prolonged hospitalization, development and progression of chronic kidney disease, and death. Early acute kidney injury treatment can improve outcomes. However, current decision support is not able to detect patients at the highest risk of developing acute kidney injury. We analyzed routinely collected emergency department (ED) data and developed prediction models with capacity for early identification of ED patients at high risk for acute kidney injury.

Methods: A multisite, retrospective, cross-sectional study was performed at 3 EDs between January 2014 and July 2017. All adult ED visits in which patients were hospitalized and serum creatinine level was measured both on arrival and again with 72 hours were included. We built machine-learning-based classifiers that rely on vital signs, chief complaints, medical history and active medical visits, and laboratory results to predict the development of acute kidney injury stage 1 and 2 in the next 24 to 72 hours, according to creatinine-based international consensus criteria. Predictive performance was evaluated out of sample by Monte Carlo cross validation.

Results: The final cohort included 91,258 visits by 59,792 unique patients. Seventy-two–hour incidence of acute kidney injury was 7.9% for stages greater than or equal to 1 and 1.0% for stages greater than or equal to 2. The area under the receiver operating characteristic curve for acute kidney injury prediction ranged from 0.81 (95% confidence interval 0.80 to 0.82) to 0.74 (95% confidence interval 0.74 to 0.75), with a median time from ED arrival to prediction of 1.7 hours (interquartile range 1.3 to 2.5 hours).

Conclusion: Machine learning applied to routinely collected ED data identified ED patients at high risk for acute kidney injury up to 72 hours before they met diagnostic criteria. Further prospective evaluation is necessary. [Ann Emerg Med. 2020;■:1-14.]

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INTRODUCTION

Background and Importance

Acute kidney injury is a common clinical syndrome strongly associated with excess morbidity and mortality.[1,2] Patients who develop it are at elevated risk for prolonged and more expensive hospitalization, chronic kidney disease and dialysis, major adverse cardiovascular events, and death.[3,4] Currently, acute kidney injury diagnosis is made in accordance with the elevation of serum creatinine (sCr) concentration or reduction in urinary output, both of which are indirect markers of renal function and may lag days behind the onset of injury and functional decline.[5-7] These limitations contribute to underdiagnosis and make detection of patients at elevated risk for acute kidney injury particularly challenging in an emergency department (ED) setting. Furthermore, pairing early detection and acute kidney injury risk stratification with renally focused clinical decision support has been shown to decrease acute kidney injury incidence and severity and drive improvements in acute kidney injury–related clinical outcomes in the inpatient setting.[8-12]

Widespread adoption of the electronic health record and rapid advancements in computing capability for large-scale data have generated new opportunities for prediction and prevention of disease through high-content data analytics and electronic health record–integrated clinical decision support.[13,14] Acute kidney injury is particularly well suited for data-driven approaches and has been identified as an

Editor's Capsule Summary

What is already known on this topic

Acute kidney injury, although not always evident at hospitalization, is common, costly, and a source of morbidity.

What question this study addressed

Can a machine-learning approach use data commonly collected early in an emergency department (ED) visit to predict acute kidney injury that occurs during hospitalization?

What this study adds to our knowledge

Among a large cohort of hospitalized patients, a machine-learning approach predicted kidney injury with modest sensitivity and specificity only 1.7 hours into an ED visit.

How this is relevant to clinical practice

Machine-learning processes may enable earlier and more accurate predictions of patients' clinical courses than clinical decision rules and so provide new opportunities for timely intervention.

important target for electronic health record–based predictive modeling.[15] Although a number of acute kidney injury prediction models have been reported recently, most were derived and validated in specific patient populations, including those undergoing cardiac surgery or catheterization,[16,17] children,[18] elderly adults,[19] or the critically ill.[20] Those developed in unselected populations have been optimized for use in the inpatient setting.[21-25] To date, none have demonstrated the capacity to make reliable predictions in the timeframe required to support acute kidney injury–focused decisionmaking during the ED encounter.

Goals of This Investigation

In this study, we developed and validated a series of prediction models for early identification of ED patients at elevated risk for postencounter acute kidney injury. These models apply machine-learning methods to routinely available electronic health record data and identify patients who are likely to develop sCr-defined acute kidney injury within 24, 48, or 72 hours. We hypothesized that a machine-learning-based classifier leveraging routinely available electronic health record data could accurately estimate risk for postencounter acute kidney injury shortly after ED arrival.

MATERIALS AND METHODS

Setting and Selection of Participants

Predictive models were developed and cross validated with a cohort of patient visits to 3 EDs within a university-based health system between January 1, 2014, and July 31, 2017. These included 2 urban academic EDs and a suburban community ED whose mean annual patient volume during the study period was 62,600, 51,000, and 54,300, respectively. Adult patients (>18 years) who were hospitalized after treatment at 1 of the 3 study site EDs with at least 1 sCr measurement performed during the ED encounter and a repeated measure within 72 hours of ED departure were included in the study. Excluded were patients with a history of dialysis or initial sCr concentration greater than 4.0 mg/dL (to avoid inclusion of patients with baseline severe renal dysfunction) and patients with initial sCr concentration less than 0.4 mg/dL (to avoid misclassification of random laboratory error as acute kidney injury). The Johns Hopkins Medicine Institutional Review Board approved this study.

Methods of Measurement

Outcome and predictor data were collected from a relational database that underlies the common electronic health record (Epic, Verona, Wisconsin, USA) used at all 3 study sites. Predictor variables were selected according to previously published literature and clinical judgment and were reviewed by a team of clinicians and data scientists for face validity and collection reliability (eg, assessments of descriptive statistics for each variable).[7,26,27] The prediction point established for each patient in the cohort was the time of the first metabolic panel result. This time was chosen because it allowed prediction early in the ED treatment course and after numerous important predictor data were gathered. All predictor data were available in the electronic health record before the prediction time, and outcomes were measured with sCr measurements obtained after the prediction point but within the model-specific outcome window (24, 48, or 72 hours).

Outcome Measures

The primary outcomes predicted were stage 1 and 2 acute kidney injury at 24, 48, and 72 hours after ED evaluation. Definition of acute kidney injury was based on international consensus criteria published by the Kidney Disease Improving Global Outcomes work group guidelines, which define acute kidney injury stage 1 or greater as any acute increase in sCr concentration greater than or equal to 0.3 mg/dL or 1.5 times baseline; acute kidney injury stage 2 or greater is defined as any acute

increase in sCr concentration greater than or equal to 2.0 times baseline.[7] Baseline sCr concentration was defined as sCr concentration measured at ED arrival. Outcomes calculations were performed by comparing baseline with the highest sCr recorded within the respective outcome window. Although Kidney Disease Improving Global Outcomes guidelines also include urinary-output-based criteria for acute kidney injury diagnosis and staging, these were not used for model development because urinary output is not routinely recorded in the ED setting. Models were developed for 3 distinct prediction horizons (24, 48, and 72 hours) according to previously described lags between initial renal injury and maximal elevation of sCr concentration and to investigate how far into the future reliable predictions could be made by using only data available early in the ED encounter.[5,6]

Data used for prediction were limited to those routinely gathered and stored in the electronic health record during the course of ED care delivery. These included patient demographics (age, sex, race, and ethnicity), arrival mode (ambulance and walk-in), vital signs (temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure, and oxygen saturation), chief complaint, medical history and active medical problems (identified according to *International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10]* codes), and laboratory test results (albumin, anion gap, bicarbonate, blood urea nitrogen, ratio of blood urea nitrogen to creatinine, creatinine, glucose, hemoglobin, lactic acid, platelets, potassium, sodium, troponin, WBC count, and urine specific gravity). Predictor data must have been recorded and available in the electronic health record before prediction to be included.

Predictor data were prepared with discretization of continuous measures, basic temporal analyses, and feature selection methods for high-dimensional data before the predictive model was fitted. The premodel fit processing for each type of electronic health record data was performed as follows: sex, race, ethnicity, and arrival mode were input as categorized predictors. Age was discretized into 10-year increments. Vital signs were discretized as normal or gradations of abnormal by using a previously defined schema based on physiology-based criteria.[28-31] Chief complaints entered directly into the electronic health record from a structured pick list (819 discrete complaints) were grouped into clinically meaningful categories with a previously defined schema[28,29] adapted for the ED from the Centers for Disease Control and Prevention Reason-for-Visit Classification List and Agency for Healthcare Research and Quality Clinical Classification Software.[32,33] Least absolute shrinkage and selection operator regression was then used to identify specific electronic health record–entered complaints with predictive value separate from their categories to be input to the model.[34] Active medical problems (10,067 unique *ICD-10* codes) were processed with least absolute shrinkage and selection operator to select those with independent predictive value. Only active medical problems identified by least absolute shrinkage and selection operator were input into the final cross-validated model. Laboratory data available between ED arrival and the prediction time were normalized from their natural bounded range (capping extreme values at the first and 99th percentile for stability) to a standardized range between 0 and 1.

Missing data were not excluded or imputed according to our hypothesis that these data may not be missing at random.[35,36] Furthermore, previous experience in developing machine-learning-based technology in emergency care environments has demonstrated that inclusion of missing data, instead of exclusion or imputation, produces better and more reliable prospective predictive performance.[28,29] Missing values were assigned their own category for demographics, arrival mode, and chief complaint. All vital signs and laboratory results were filtered to minimum and maximum values, and a separate binary variable was generated to indicate whether values for any individual vital sign or laboratory result were unavailable at prediction.

Primary Data Analysis

Ensemble-based decision tree learning algorithms (random forest) were trained on the reference cohort to predict the onset of acute kidney injury and were evaluated with 10-fold cross validation, repeated 10 times to minimize the variance in prediction performance estimations (Monte Carlo cross validation).[37] Within each of the 10 repetitions, the cohort was randomly distributed into training (90% of data) and validation (10% of data). The models learned from the training data set, and their performance was assessed on the validation data set, iteratively. During training, the random forest algorithm executes a randomized sampling process to train a set of individual decision trees (eg, 500) and aggregates output to produce a single probabilistic prediction for each outcome.[38] Six distinct models were generated and evaluated, one for each level of acute kidney injury severity ($\geq$stage 1 or $\geq$stage 2) and prediction horizon (24, 48, or 72 hours). The stepwise process composed of data preparation (including feature engineering), model training, and out-of-sample model evaluation that was used for development and testing of each model is shown in Figure 1. Under this

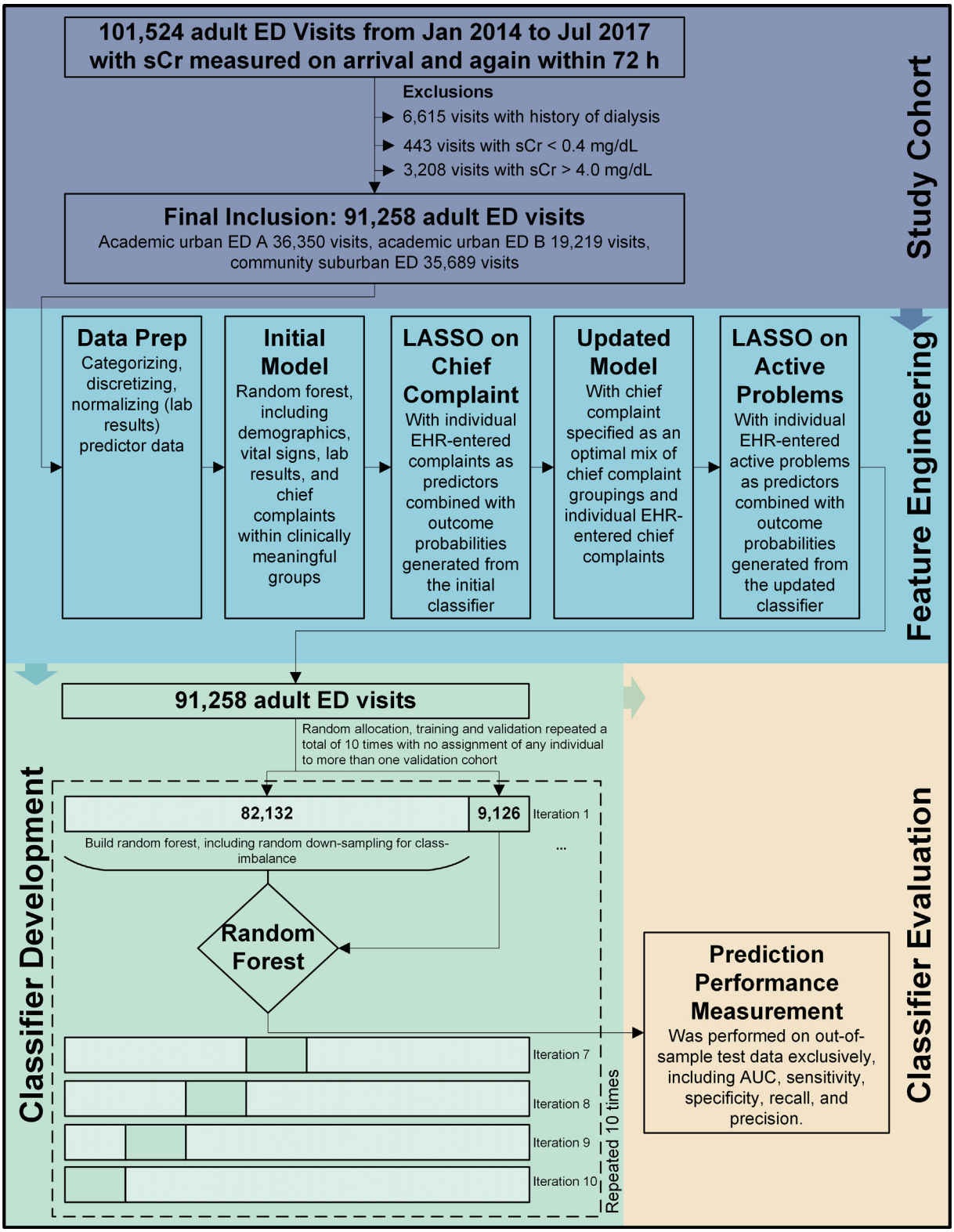

Figure 1. Study cohort and model development scheme. *LASSO*, Least absolute shrinkage and selection operator; *EHR*, electronic health record.

framework, random forest models can learn from an entire cohort while yielding out-of-sample predictions for all observations across the 10-fold cross validations generated at random. Model performance was exclusively measured

and reported for predictions made when observations fell within test sets. Random forest hyperparameter optimization was performed by grid search to identify optimal number of trees, number of features at each split, and size of the terminal nodes, but default settings exhibited highest performance and were selected for final model development. All statistical analyses were performed in R (version 3.5.3) with the freely available statistical packages randomForest (version 4.6-14) and caret (version 6.0-80).[39,40]

RESULTS

Characteristics of Study Subjects

Our initial patient cohort included 101,524 adult ED encounters wherein at least 1 sCr measurement was made during the ED encounter and again in the inpatient setting within 72 hours; 10,266 of these encounters met exclusion criteria (Figure 1). The final patient cohort included 91,258 ED encounters by 59,792 unique patients (Table 1). The overall incidence of acute kidney injury at 72 hours, stage 1 or greater, was 7.9%, whereas the overall incidence of acute kidney injury stage 2 or greater was 1.0%. Rates of acute kidney injury stage 1 were slightly higher at the 2 urban EDs than at the community ED; rates of acute kidney injury stage 2 were similar across all EDs. Demographics were similar, although there was some variation in race and ethnicity and in age at the extremes across sites. Vital signs, most common complaints, medical history, active medical problems, and laboratory results were similar between EDs.

Main Results

For all models, acute kidney injury risk prediction was triggered at a median of 1.7 hours (interquartile range 1.3 to 2.5 hours) after ED arrival, whereas the median ED length of stay was 9.2 hours. The prediction performance of all models was robust, as shown in Table 2. Overall model prediction performance, as measured by area under the receiver operating characteric (ROC) curve, was highest for prediction of stage 2 acute kidney injury within 24 hours (0.81; 95% confidence interval 0.80 to 0.82) and lowest for prediction of stage 1 acute kidney injury within 72 hours (0.74; 95% confidence interval 0.74 to 0.75). There were nonsignificant trends toward higher sensitivity for prediction of stage 1 acute kidney injury and higher specificity for prediction of stage 2 acute kidney injury. In general, prediction performance measures declined for all models as prediction horizon widened. Multiple operating points and associated precision-recall curves for prediction of stage 1 acute kidney injury are shown in Figure E1 (available online at http://www.annemergmed.com). Although sensitivity and specificity declined as prediction horizon widened (Table 2), model precision (positive predictive value) increased in parallel with cumulative incidence of acute kidney injury (2.9%, 6.0%, and 7.9% at 24, 48, and 72 hours, respectively).

Predictor variable importance, measured by mean decrease in accuracy, is shown in Figure 2 for the 10 top-performing predictors (among 131 total predictors). Baseline renal function, as indicated by sCr concentration, was the most important predictor for acute kidney injury stage 1 or greater for all prediction horizons, followed very closely by glucose concentration, markers of acid-base status (eg, bicarbonate, anion gap), albumin, and diastolic blood pressure. Markers of acid-base status were the most important predictors of severe (≥stage 2) acute kidney injury, and played a more prominent predictive role in these models than in those for milder forms of acute kidney injury. Glucose concentration maintained very high importance across all models.

LIMITATIONS

This study has several important limitations. First, outcomes predicted were laboratory based; because of our retrospective study design and lack of consistent long-term outcomes data for all patients, we were unable to reliably determine which cases of sCr-defined acute kidney injury were persistent versus transient and which patients went on to develop chronic kidney disease and renal failure–associated adverse clinical events. However, a large number of well-powered studies using definitions similar to those used here have shown that sCr-defined acute kidney injury, even when mild or transient, is a clinically important outcome independently associated with increased risk for progression to chronic kidney disease, dialysis, and death.[1,41-44] Second, all models were derived and validated with data from a single health system. Although this weakness was minimized through use of large training and testing data sets and the inclusion of ED encounters from a variety of practice settings, external validation is an important ongoing objective. Third, these models were developed and validated in a selected group of ED patients with measured outcomes (eg, hospitalized patients with repeated sCr measurement). Outcomes data are often unavailable for patients who are discharged into the community after their ED encounter, challenging the development and validation of outcomes-driven risk estimation tools that can be broadly applied in emergency medicine. Methods to properly account for

Table 1. Patient characteristics and outcomes.

Population	Urban ED A	Urban ED B	Community ED	Overall
Cohort size, No.	36,350	19,219	35,689	91,258
Predicted outcomes, AKI stage, %				
1	9.4	8.1	6.3	7.9
2	1.2	1.0	0.9	1.0
Demographics and arrival mode, %				
Age, y				
18–29	11	6.0	6.0	8.0
30–39	12	10	8	10
40–49	14	11	10	12
50–59	24	21	16	20
60–69	19	20	17	19
70–79	12	15	18	15
80–89	6.0	12	18	12
>90	2.0	4.0	7.0	4.0
Sex, women	50	52	54	52
Race, white	37	68	63	54
Race, black	56	26	25	37
Ethnicity, Hispanic	3.0	3.0	3.0	3.0
Arrival, ambulance	29	57	47	44
Shortness of breath	12	17	13	14
Abdominal pain	12	10	14	12
Chest pain	9.0	11	9.0	10
Psychiatry	5.0	2.0	1.0	3.0
Nausea, vomiting, or diarrhea	4.0	4.0	5.0	4.0
Primary care physician	97	95	97	97
Medical history, %				
Diabetes mellitus	0.2	0.1	0.0	0.1
Chronic kidney disease	4.3	5.1	2.6	4.0
Acute kidney injury	1.0	0.9	0.5	1.0
Thrombocytopenia	1.1	0.8	0.6	1.0
Hyperlipidemia	12	18	10	13
Hypertension	53	60	61	58
Heart failure	10	13	9	11

Vital signs (median, IQR), average				
Pulse rate, beats/min	86.4 (85, 73–98)	87.1 (85, 73–99)	84.2 (82, 71–95)	85.6 (84, 72–97)
Respiratory rate, breaths/min	19.6 (18, 16–20)	19.6 (18, 17–21)	18.6 (18, 16–20)	19.2 (18, 16–20)
Systolic blood pressure, mm Hg	128.3 (125, 110–144)	127.1 (125, 111–142)	127.1 (126, 111–141)	142 (126, 111–142)
Diastolic blood pressure, mm Hg	72 (70, 61–81)	71 (70, 60–80)	69.2 (68, 59–78)	70.5 (69, 60–79)
Oxygen saturation, %	97.3 (98, 96–99)	96.9 (97, 95–99)	96.7 (97, 95–99)	96.9 (97, 95–99)
Temperature, °F	98.1 (97.9, 97.3–98.6)	98.3 (98.2, 97.9–98.6)	98.4 (98.2, 97.9–98.7)	98.3 (98.2, 97.7–98.6)
Active problems and laboratory tests, average (median, IQR); % of unobserved				
Active problems	7 (4, 1–10); 0	8 (5, 1–12); 0	4 (2, 0–6); 0	7 (4, 1–10); 0
Creatinine, mg	1.1 (1, 0.8–1.3); 0	1.1 (1, 0.8–1.4); 0	1.1 (1, 0.7–1.3); 0	1.1 (1, 0.8–1.3); 0
Blood urea nitrogen, mg/dL	18.9 (15, 10–22); 0	19.4 (16, 11–23); 0	21.3 (17, 12–25); 0	19.9 (16, 11–24); 0
BUN-to-creatinine ratio	16.5 (15, 11–20); 0.3	16.9 (15, 12–20); 0	19.2 (17.5, 13.3–23); 0	17.6 (16, 12–21); 0
Glucose, mg/dL	143.8 (111, 95–146); 0	137.9 (109, 94–139);0	150.5 (121, 103–158); 0	147.5 (116, 98–153); 0
Anion gap, mEq/L	16 (15, 13–18); 0.3	9.1 (9, 7–11); 0.4	14.3 (13.9, 11.9–16); 0.1	14 (12, 11–16.2); 0
Albumin, g/dL	3.9 (4, 3.6–4.4); 3.1	3.4 (3.5, 3.1–3.8); 1.6	4 (4.1, 3.7–4.4); 3.9	3.9 (3.9, 3.5–4.3); 3
Potassium, mEq/L	4.2 (4.2, 3.8–4.6); 6.5	4 (4, 3.7–4.3); 18	4.2 (4.2, 3.8–4.5); 2.9	4.2 (4.1, 3.8–4.5); 7
Sodium, mEq/L	138.1 (139, 136–141); 0.1	138.4 (139, 136–141); 0	138.1 (139, 136–142); 0	138.2 (139, 136–141); 0
Bicarbonate	4,820 (4,825, 4,387–5,442); 0	5,463 (5,442, 5,034–6,020); 0	5,208 (5,244, 4,825–5,650); 0	5,098 (5,244, 4,607–5,650); 0
Troponin T, ng/dL	Not applicable;100	Not applicable;100	0.02 (0, 0–0.03); 79	0.02 (0, 0–0.03); 92
Troponin I, ng/mL	0.16 (0, 0–0.05); 83	0.14 (0, 0–0.03); 48	Not applicable;100	0.21 (0, 0–0.05); 82
Urine specific gravity	1.02 (1.01, 1.01–1.02); 84.7	1.02 (1.02, 1.01–1.02); 89.7	1.02 (1.01, 1.01–1.02); 85.5	1.02 (1.02, 1.01–1.02); 86
Hemoglobin, g/dL	11.7 (12, 10–13.6); 11.9	12.3 (12.5, 10.8–14); 9.3	12.2 (12.4, 10.7–13.9); 10.9	12 (12.3, 10.4–13.8); 11
Platelets, 10^9/L	247.7 (233, 176–302); 12.2	241.8 (23, 179–289); 9.3	234.4 (222, 174–280); 10.9	242.3 (228, 175–290); 11
WBC count, 10^9/L	9.6 (8.3, 6.1–11.5); 11.9	10.3 (9.1, 6.8–12.3); 9.3	10.4 (9.2, 6.8–12.6); 10.9	10 (8.8, 6.5–12.1); 11
Lactate, mmol/L	2.3 (1.8, 1.3–2.6); 62.7	2.6 (2, 1.4–2.9); 67	2.2 (1.8, 1.2–2.5); 85.5	2.4 (1.8, 1.3–2.7); 73

AKI, Acute kidney injury; *IQR*, interquartile range; *BUN*, blood urea nitrogen; *WBC*, white blood cells.

Table 2. Model prediction performance statistics.

Outcome and Prediction Horizon	AUC	Sensitivity	Specificity	Time to Prediction
AKI stage ≥1				
Within 24 h	0.80 (0.79–0.80)	0.72 (0.71–0.73)	0.73 (0.72–0.73)	1.7 (1.3–2.5)
Within 48 h	0.76 (0.75–0.76)	0.70 (0.70–0.71)	0.68 (0.68–0.68)	1.7 (1.3–2.5)
Within 72 h	0.74 (0.74–0.75)	0.69 (0.69–0.69)	0.67 (0.67–0.67)	1.7 (1.3–2.5)
AKI stage ≥2				
Within 24 h	0.81 (0.80–0.82)	0.71 (0.70–0.73)	0.76 (0.75–0.76)	1.7 (1.3–2.4)
Within 48 h	0.77 (0.77–0.78)	0.69 (0.68–0.70)	0.71 (0.70–0.71)	1.7 (1.3–2.5)
Within 72 h	0.75 (0.74–0.75)	0.68 (0.67–0.69)	0.68 (0.68–0.69)	1.7 (1.3–2.4)

AUC, Area under the ROC curve.
Performance statistics represented as averages and 95% confidence intervals in parentheses (time performance represented by medians with IQRs in parentheses). AKI per 2012 Kidney Disease Improving Global Outcomes definition.

these data are needed and this topic is an active focus of investigation by our research group. Finally, although the ultimate goal of this work is to improve patient outcomes through prediction-driven acute kidney injury–focused clinical decision support, the models reported here have not been integrated into ED clinical work flow and their capacity for clinical influence has yet to be evaluated.

Beyond this study, there are advantages and limitations to the application of machine-learning methods to electronic health record data for clinical risk stratification, with direct implications for generalizability. Machine-learning models can be derived and validated with large-scale data from a single population, generating predictions that are optimized to the local population characteristics (eg, demographics, acute and chronic disease prevalence, social determinants of health), clinician practice patterns, and informatics environment that make individual EDs unique. The exact model developed for and validated in one ED population is often not intended to be used directly in others. This contrasts with more traditional risk stratification tools (eg, clinical decision rules), which are often more portable but can have shortcomings when applied in populations or practice settings that differ in meaningful ways from those in which they were originally derived and externally validated. Machine-learning models can be optimized for use in new environments through retraining and validation using locally derived data sets. Indeed, our research team has previously adapted multiple machine-learning models derived in one population to be applied and drive clinical decision support in another by retraining with local data.[28,45,46] In addition, the process by which individual models are developed—including data procurement and normalization, feature engineering, and algorithm development and evaluation (Figure 1)—can be highly generalizable. The methods described here are transferable to other clinical contexts and to a wide array of clinical conditions encountered in the ED setting.

DISCUSSION

In this study, we derived and validated a series of machine-learning models with capacity to identify ED patients at elevated risk for acute kidney injury up to 72 hours earlier than possible with traditional diagnostic approaches.[47-49] We were able to generate highly reliable acute kidney injury risk estimates, relying exclusively on data that already resided within the electronic health record, and were able to do so less than 2 hours after patient arrival to the ED. Although other acute kidney injury prediction models have been reported,[20-25] none make predictions at such an early point in the care continuum, and none were developed with the explicit goal of informing decision support that targets ED-based acute kidney injury detection and treatment in the ED. Development of clinical decision support with this target in mind is important because ED clinicians now set treatment trajectories for a majority of hospitalized patients and for an even greater number of patients discharged into the community.[50,51]

Reduction of acute kidney injury–related adverse health and economic effects is urgently needed.[52,53] Recent estimates derived from the National Inpatient Sample suggest costs of acute kidney injury exceed $5.4 billion annually, making it the second most expensive condition in US health care, just behind sepsis, at $7.7 billion.[54] Although cases of severe acute kidney injury requiring dialysis are the most expensive, they occur infrequently and account for less than a quarter of all acute kidney injury costs. Most costs are incurred by patients with relatively mild acute kidney injury. For example, Zeng et al[55] found

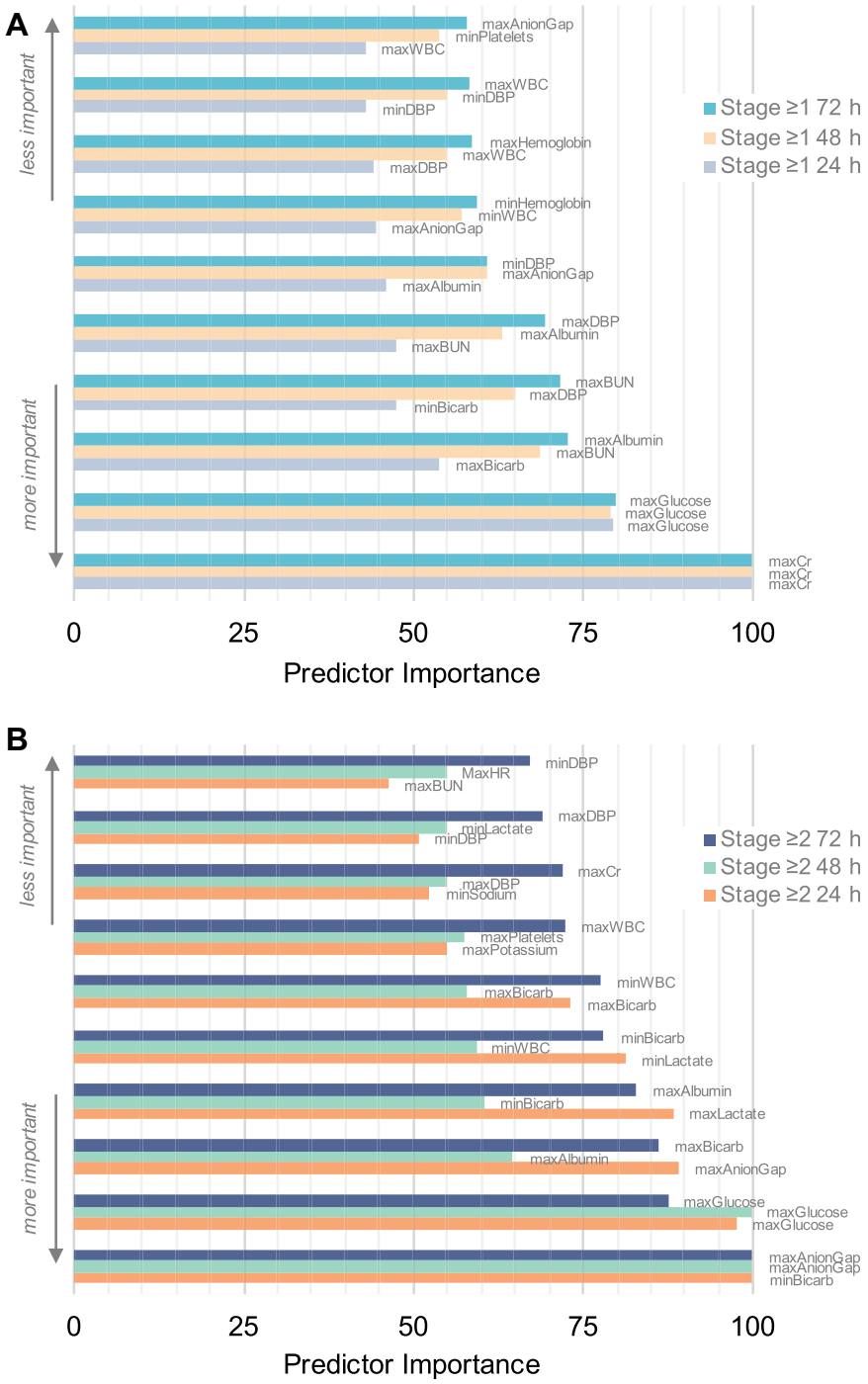

Figure 2. Predictor variable importance. The 10 leading predictors for acute kidney injury stage greater than 1 (*A*) and stage greater than 2 (*B*) are shown. *DBP*, Diastolic blood pressure; *Cr*, creatinine; *HR*, pulse rate.

that even stage 1 acute kidney injury (defined by an increase in sCr concentration as low as 0.3 mg/dL, or 1.5 to 1.9 times baseline) increased length of hospital stay by an average of 2.5 days and costs by $5,400. This mildest form of acute kidney injury was also associated with a 2-fold increased risk for death, even after adjusting for demographics and comorbid illness; risk was increased 3- and 10-fold for stages 2 and 3 acute kidney injury, respectively. Even transient acute kidney injury, a condition characterized by increases in sCr concentration that normalize over time and thought of by many clinicians as benign, has also been associated with significant increases in short- and long-term adverse events, including prolonged and more expensive hospitalization, chronic

kidney disease, and death.[41-43] Although the incidence and effect of acute kidney injury in unselected ED populations are less well studied and understood, several recent reports suggest both may be higher than previously appreciated.[56,57] This notion is supported by what is to our knowledge the only ED-based prospective study of acute kidney injury to date, wherein rates of postencounter acute kidney injury were similar in patients who were hospitalized and discharged home.[3] In this same study, development of acute kidney injury was associated with markedly increased risk for chronic kidney disease, myocardial infarction, stroke, and death at 1 year.

There are no effective treatments to reverse acute kidney injury once it occurs. Thus, harm-reduction efforts must focus on early recognition, halting disease progression, and preventing new cases from occurring.[7] Multiple national and international societies have advocated early identification of patients with or at increased risk for developing acute kidney injury, and several have provided clear and actionable recommendations for their care.[15,49,58,60] Invasive or costly measures, such as initiation of renal replacement therapy or ICU admission, are recommended only for patients who have already manifested severe acute kidney injury. Recommendations for patients with mild to moderate acute kidney injury, and for those deemed to be at elevated risk for developing acute kidney injury, are relatively simple and include guidance to search for potential causes of kidney injury and remedy them if found, to monitor and optimize fluid status, and to prevent ongoing injury through treatment of hyperglycemia, avoidance of nephrotoxic agents when possible, and adjustment of medication dosing based on renal function, when appropriate.[49,59,60]

Recently, translation of these recommendations into practice has shown that disease progression and mortality can be reduced through acute kidney injury–targeted clinical decision support.[8-12,61,62] The effectiveness of electronic detection and clinician alerting for patients who meet Kidney Disease Improving Global Outcomes sCr-based criteria for acute kidney injury has been evaluated in the adult inpatient setting. Effects of stand-alone alerts have been mixed, with one group reporting no change in clinician practice or patient outcome and another reporting a sustained decrease in hospital length of stay, progression to dialysis, and inhospital mortality.[8,63] Another group paired electronic acute kidney injury detection with provision of clinical decision support to drive completion of an acute kidney injury care bundle and found that care bundle completion was associated with decreased progression to higher-severity acute kidney injury and death.[10,61] Care bundles were derived from the evidence-based recommendations for acute kidney injury described earlier (eg, search for and remedy causes of acute kidney injury, optimize fluid status, and prevent ongoing injury), all of which could be readily incorporated into ED practice. In all of these studies, acute kidney injury alerts were triggered after patients met sCr-based criteria for acute kidney injury, a signal that may be delayed by several days from initial renal insult, and it is likely that intervention at an earlier point could have even greater effect.[5,6]

Several studies have now shown that acute kidney injury can also be prevented through early risk estimation and provision of renally targeted clinical decision support before sCr-based acute kidney injury criteria are met. The first of these used an electronic health record surveillance algorithm that monitored medication prescribing practices to identify pediatric inpatients at risk for nephrotoxin-mediated acute kidney injury.[9,64] This algorithm, paired with alerts and clinical decision support for treating clinicians, resulted in decreased rates of nephrotoxin exposure (38% reduction) and acute kidney injury (64% reduction). These reductions were sustained during multiple years and were not associated with unintended adverse effects related to avoidance of or delay to indicated treatments (eg, initiation of antimicrobial therapy).[9] These findings are particularly relevant to the ED practice setting, in which initial medication prescribing decisions are made for a majority of patients and are known to be independently associated with subsequent development of acute kidney injury.[65] Another group paired acute kidney injury care bundles similar to those described earlier with a static acute kidney injury prediction rule in adults, deployed at inpatient admission to reduce incidence of hospital-acquired acute kidney injury and inhospital mortality effectively.[62,66,67] The acute kidney injury prediction rule used in this study relied on variables not reliably captured in the electronic health record, challenging automated deployment across practice settings and direct comparison with the acute kidney injury predictive models we have reported here. However, our models were designed to make predictions at a much earlier point and exhibited higher levels of predictive accuracy (area under the ROC curve) than reported for the rule-based scoring system,[66] suggesting similar or superior effects could be achieved through their use. Finally, acute kidney injury care bundles have recently been paired with the only Food and Drug Administration–approved biomarker-based test (Nephrocheck) for early detection of renal injury to decrease incidence and progression of acute kidney injury in patients undergoing major surgery.[11,12] Although biomarkers may improve time to detection of acute kidney injury in general populations in the future,

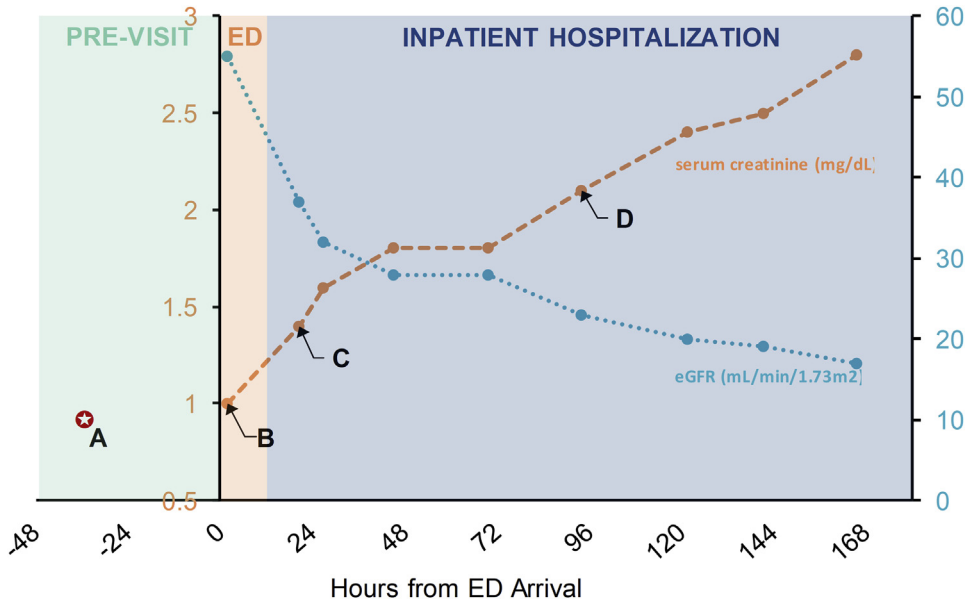

Figure 3. Acute kidney injury use case sample. Selected patient encounter demonstrating acute kidney injury prediction in relation to hospital visit progression and renal function over time. *A*, Reported illness onset was 40 hours before ED arrival. *B*, Acute kidney injury prediction was generated 2.0 hours after ED arrival and 6.6 hours before ED departure. *C*, Kidney Disease Improving Global Outcomes criteria for stage 1 acute kidney injury were met 18.6 hours after acute kidney injury prediction. *D*, Kidney Disease Improving Global Outcomes criteria for stage 2 acute kidney injury met 94.2 hours after acute kidney injury prediction.

they remain costly and not widely available.[68] The machine-learning models described here perform at a level of predictive accuracy similar to that of Nephrocheck and could be used to generate real-time patient-level acute kidney injury risk estimates for all comers at a nominal cost.[69,70]

The potential clinical utility of the models described here is illustrated in Figure 3, using an explanatory patient encounter from our cohort. This patient, an elderly woman who initially presented with chest pain and was later found to have a surgical wound infection, did not meet Kidney Disease Improving Global Outcomes criteria for acute kidney injury until 18.6 hours after ED arrival and more than 2 days after her reported illness onset. All clinical decisions made during her ED encounter and during the early portions of her inpatient stay were made under the assumption of near-normal renal function. On hospital day 2, she was severely oliguric, with increasing sCr concentration. Nephroprotective measures were taken, including discontinuation of previously initiated nephrotoxic medications and optimization of fluid status, with close monitoring of urinary output. Our model accurately predicted that she would develop acute kidney injury only 2 hours after she arrived in the ED. Individualized prediction-based and acute kidney injury–focused clinical decision support, provisioned early in her care continuum, might have enabled more optimal renally focused clinical decisionmaking and limited the progression of her disease. Decisions that could have been affected by such clinical decision support in this single patient encounter included earlier treatment of hyperglycemia, earlier attention to fluid status optimization, discontinuation of nonessential home medications with nephrotoxic properties, and selection of an empirical antibiotic treatment regimen that minimized potential for nephrotoxicity while continuing to provide adequate antimicrobial coverage.[49,58,59]

This patient would have been identified by our models as exhibiting increased risk for acute kidney injury and would have received appropriately targeted nephroprotective clinical decision support. The exact performance of our model in clinical practice would be determined by final selection of prediction horizon (ie, 24, 48, or 72 hours) and desired model precision (Figure E1, available online at http://www.annemergmed.com). However, under all scenarios, many patients who did not develop acute kidney injury would also have been targeted with nephroprotective clinical decision support (ie, false-positive results), and a smaller proportion of those who did develop acute kidney injury would not have been targeted. Although the predictive performance of these models may be improved through ongoing research and refinement, the sensitivities and specificities reported here exceed those of a

static clinical prediction rule that has been proven effective to improve acute kidney injury–related outcomes in the inpatient setting. Acute kidney injury model predictive performance is also similar to that reported for the only Food and Drug Administration–approved biomarker-based assay available for early detection of acute kidney injury.[66,69,70]

In summary, machine-learning methods applied to electronic health record data identified ED patients at high risk for acute kidney injury up to 72 hours before they met diagnostic criteria. The models developed here, when paired with nephroprotective point-of-care clinical decision support, have the potential to improve outcomes for this at-risk patient population.

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Author affiliations: From the Department of Emergency Medicine (Martinez, Levin, Klein, Hinson), Division of Health Sciences Informatics (Martinez, Levin), and Department of Medicine, Division of Nephrology (Parikh, Menez), Johns Hopkins University, Baltimore, MD; the Center for Disease Dynamics, Economics and Policy, Washington, DC (Klein); and the Department of Emergency Medicine, Yale University, New Haven, CT (Taylor).

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