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Artificial intelligence and machine learning for predicting acute kidney injury in severely burned patients: A proof of concept

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ARTICLE INFO

Article history:
Accepted 26 March 2019

Keywords:
Algorithm
Creatinine
k-Nearest neighbor
Neutrophil gelatinase associated lipocalin
Urine output

ABSTRACT

Background: Burn critical care represents a high impact population that may benefit from artificial intelligence and machine learning (ML). Acute kidney injury (AKI) recognition in burn patients could be enhanced by ML. The goal of this study was to determine the theoretical performance of ML in augmenting AKI recognition.
Methods: We developed ML models using the *k*-nearest neighbor (*k*-NN) algorithm. The ML models were trained-tested with clinical laboratory data for 50 adult burn patients that had neutrophil gelatinase associated lipocalin (NGAL), urine output (UOP), creatinine, and N-terminal B-type natriuretic peptide (NT-proBNP) measured within the first 24 h of admission.
Results: Half of patients (50%) in the dataset experienced AKI within the first week following admission. ML models containing NGAL, creatinine, UOP, and NT-proBNP achieved 90–100% accuracy for identifying AKI. ML models containing only NT-proBNP and creatinine achieved 80–90% accuracy. Mean time-to-AKI recognition using UOP and/or creatinine alone was achieved within 42.7 ± 23.2 h post-admission vs. within 18.8 ± 8.1 h via the ML-algorithm.
Conclusions: The performance of UOP and creatinine for predicting AKI could be enhanced by with a ML algorithm using a *k*-NN approach when NGAL is not available. Additional studies are needed to verify performance of ML for burn-related AKI.

1. Introduction

Artificial intelligence (AI) is forecasted to be a $3.9 trillion industry by 2022 [1,2]. Machine learning (ML) platforms are now readily accessible and various platforms (e.g., Scikit-Learn, Apple's Turi Create and Core ML, and Google's Tensor Flow, etc) are now being used to build these very relevant and powerful ML models that could ultimately enhance patient care and health care delivery. However, the use of such AI/ML tools in health care disciplines remains embryonic, with initial efforts resulting in more questions than definitive solutions for improving health outcomes [3–5].

Burn critical care represents a high impact population that may benefit from AI/ML [6]. Early recognition of sepsis and organ dysfunction, both common burn sequelae, could be

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https://doi.org/10.1016/j.burns.2019.03.021

exploited by AI/ML to integrate various sources of information (e.g., laboratory results, vital signs) into a composite, prognostic, and predictive "clinical picture" [7].

Burn-related acute kidney injury (AKI) is one such focus for AI/ML. Up to 58% of burn patients acquire AKI due to pre-renal (e.g., burn shock, sepsis) and renal mechanisms (e.g., nephrotoxic medications) of injury—with AKI common within the first week due to inadequate resuscitation during the critical first 24 h of admission [8–12]. Despite this high prevalence, early recognition remains challenging due to the reliance on serum/plasma creatinine and urine output (UOP) for diagnosing and staging AKI [13]—biomarkers that have known limitations. Creatinine has a slow half-life [14] and exhibits high biological variability [15]. Alternately, UOP may remain unchanged in critically ill patients despite decreasing glomerular filtration rate (GFR) [16].

Studies have proposed novel AKI biomarkers including neutrophil gelatinase associated lipocalin (NGAL), kidney injury marker-1 (KIM-1), tissue inhibitory of metalloprotease-2 (TIMP-2), and insulin-like growth factor binding protein-7 (IGBFP-7) to overcome the limitations of UOP and creatinine [10,11,17]. However, routine clinical use of these biomarkers remains limited due to regulatory constraints and commercial availability. Thus, advancements in burn AKI recognition remain stagnant and continue to be dependent on creatinine and UOP for many healthcare facilities across the United States. *To this end, the goal of this study was to evaluate the clinical utility for ML in augmenting the predictive power of both traditional and novel indicators of AKI.*

2. Methods

We developed and validated a ML study design that allowed us to use an existing quality database comprised of burn patients at risk for AKI. The database was derived from a hospital project to validate a NGAL biomarker assay for potential clinical laboratory implementation as a laboratory developed test. Patient population and methods of analysis are described below:

2.1. Study Population

The database consisted of 50 adult (age ≥18 years) patients with ≥20% total body surface area (TBSA) burns at risk for AKI. Plasma samples obtained as part of routine clinical basic metabolic panels were collected on the first hospital day and banked for additional testing. The focus on the first 24 h was based on burn patient AKI risk immediately following injury to guide resuscitative measures, and to standardize creatinine testing results for comparison. Specifically, plasma creatinine testing was performed via the clinical laboratory using a Jaffe-based method (Beckman Coulter, Brea, CA) at admission. Serial creatinine testing on subsequent days were based on enzymatic methods. Neutrophil gelatinase associated lipocalin (NGAL) concentrations were quantified using a commercially available enzyme-linked immunosorbant assay (Bioporto, Inc, Denmark). These NGAL results were not used for patient care. In brief, NGAL is released by neutrophils during inflammation and renally cleared [10,11]. Neutrophil gelatinase associated lipocalin clearance is reduced during AKI due to decreased GFR. Uniquely, renal tubular cells also produce NGAL during AKI—increasing both plasma and urine concentrations of NGAL through reabsorption and elimination respectively.

Given its role in cardiorenal syndrome, N-terminal pro B-type natriuretic peptide (NT-proBNP) was also measured (Roche Diagnostics, Indianapolis, IN) in the same plasma samples to complement NGAL [18]. As with NGAL, NT-proBNP results were also not reported to the healthcare providers. Paired serial UOP measurements and vital signs were also collected from the electronic medical record (EMR). Chart review was used to determine which patients experienced AKI within a one-week period following burn intensive care unit admission. Acute kidney injury was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (Table 1) [13].

2.2. ML Algorithm

The Scikit-Learn's (version 0.20.2) *k*-nearest neighbor (k-NN) algorithm (Fig. 1) was employed to build multiple ML models to classify and distinguish AKI from non-AKI cases. Briefly, *k*-NN is a non-parametric pattern recognition algorithm used for classification and regression [19]. For this project, *k*-NN classified patients as having AKI or no AKI. Input for the algorithm consisted of *k* closest training examples from the same dataset, where *k* was the value equal to the square root of the number of instances (Fig. 1). Once the data has been acquired, the training and testing steps in the *k*-NN algorithm involves the following steps: (1) data points are normalized based on established techniques [19] so that the distribution will ultimately have a mean value of 0 with a standard deviation of 1. This is achieved by subtracting the sample mean from each patient value and dividing by the standard deviation of the dataset. These data are then stored and split into training and testing sets (e.g., 80% for the training phase and 20% for the testing-validation accuracy phase or 60% for the

Table 1 – KDIGO criteria.

Stage	Serum creatinine	Urine output
1	1.5–1.9 × baseline, or ≥0.3 mg/dL increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 × baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 × baseline, or an increase ≥4.0 mg/dL, initiation of renal replacement therapy, in patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/h for ≥24 h, or anuria for ≥12 h

Abbreviations: eGFR, estimated glomerular filtration rate.

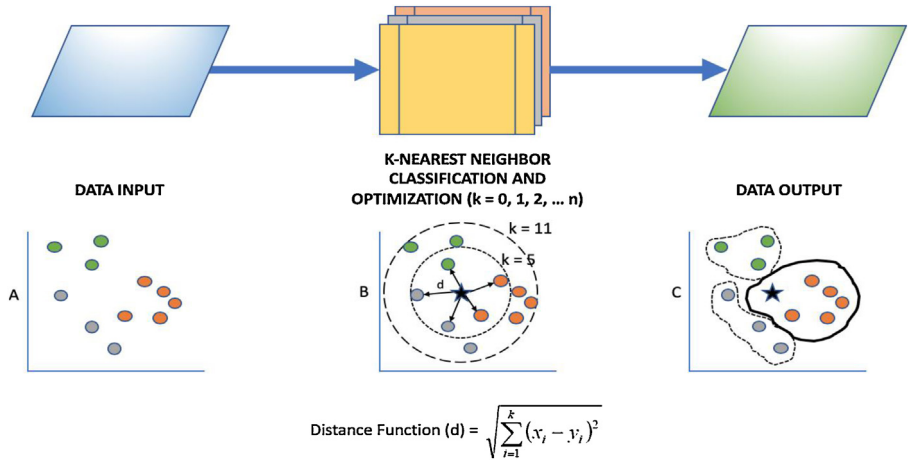

Fig. 1 – k-Nearest neighbor approach conceptual diagram.
This conceptual drawing of a k-NN classification illustrates how data is analyzed for k-nearest neighbors. From left to right, a hypothetical dataset is inputted into the algorithm (A). The algorithm then computes the distance from a reference point (black star) when k = 5 versus k = 11 neighbors, where, d is the distance function (B). This distance function weighs the "vote" for each data point relative to the reference. The data is then classified based on the algorithm (C).

training phase and 40% for the testing–validation accuracy phase, (2) distance from a new data point (black "star" in Fig. 1) is then calculated against the stored data points in the training set, (3) the data points are then sorted based on an increasing order of distance from the new data point, (4) the majority of closest points distances ("*k*": number of calculated closest points) assigns the new data point to the appropriate class. A Euclidian-based distance function (*d*) is applied to calculate the closest distance. (5) the final model is then tested against the unknown (20% or 40%) test sets to calculate the validation accuracy. The choice of k will affect the class assignment/validation accuracy (Fig. 1). (6) a "*k*" optimizer is used to find the optimal "*k*" value that generated the most accurate model.

Hence, based on the above approach, patients were then classified by a majority vote of its neighbors, with subjects then being assigned to the class most common among these nearest neighbors (*k*). A defined subset of neighbors was then selected from the dataset for having AKI or no AKI. The algorithm was also applied with and without NGAL, NT-proBNP, creatinine, or UOP to determine which biomarker provided the best predictive classification ML model across a range of *k*-values. The validation accuracy of these ML models was then assessed on an unknown set of random test cases from the original study material that were not included in the training phase of the build. To further assess each feature's independent contribution to the ML model, as noted above, feature variations and training-testing set variations (80%–20% versus 60%–40%) were used to build multiple unique ML models (e.g., models built with just two features such as NT-proBNP and NGAL or those built with three features such as NGAL, NT-proBNP and creatinine, with varying number of *k* values etc.). This approach allowed us to build 330 unique ML models (each with 22 feature and model selection variations × 15 distinct *k* values) which were then compared and contrasted to each other to assess the significance of the individual features noted above and their significance in classifying new AKI cases. Each

Table 2 – Patient demographics.

Mean (SD) variable	AKI group	Non-AKI group	P-Value
Age (years)	39.1 (49.2)	39.7 (15.5)	0.922
Burn size (% TBSA)	49.2 (24.1)	43.3 (18.9)	0.473
Gender (M/F)	20/5	19/6	0.832
Mean arterial pressure (mmHg)	78.9 (11.5)	80.1 (5.2)	0.782
Central venous pressure (mmHg)	13.3(3.4)	12.0 (7.6)	0.662
Creatinine (mg/dL)	1.21 (0.51)	0.90 (0.22)	0.066
NGAL (ng/mL)	185.1 (86.3)	110.3 (48.1)	0.013
NT-proBNP (pg/mL)	25.7 (15.4)	16.0 (15.3)	0.112
Urine output (mL/h)	81.5 (31.6)	85.7 (48.9)	0.795
Time to AKI (h)[a]	42.7 (23.2)	NA	NA

Abbreviations: F, female; KDIGO, Kidney Disease: Improving Global Outcomes; M, male; NGAL, neutrophil gelatinase associated lipocalin; NA, not applicable; NT-proBNP; N-terminal pro-B-type natriuretic peptide; TBSA, total body surface area; RRT, renal replacement therapy.
[a] Time from admission to achieving AKI based on KDIGO criteria.

ML model was initially assessed through its training set accuracy and then subsequently tested against the unknown test set (the 20% or 40% unknown cases as mentioned in train-test split method noted above) to assess its validation accuracy.

2.3. *Cross Validation studies*

In addition to the aforementioned tests and validation studies, the individual categories (i.e., those with all 4 features versus those with all combination of 3 or 2 features) were also cross validated using the Scikit-learn cross validation grid search tool which enabled us to build and compare 10 unique models within each k value in each category to yield a total of 2200 ML models. The mean accuracy for each set of these 10 models for a given k value in a given category was then analyzed.

2.4. *Statistical Analysis*

Statistical analysis was performed using JMP software (SAS Institute, Cary, NC). Descriptive statistics compared demographics between AKI versus non-AKI groups. Continuous variables were analyzed using the 2-sample t-test, while discrete variables were compared using the Chi-square test. Multivariate logistic regression was used to determine predictors of AKI with age and burn size serving as covariates. Repeated measures analysis of variance was used for time series data. A p-value <0.05 was considered statistically significant. Receiver operator characteristic (ROC) analysis was also performed to compare AKI biomarker performance.

3. Results

Fifty percent of patients (25/50) in the dataset experienced AKI within the first week of hospital stay based on KDIGO criteria. Patient demographics are summarized in Table 2. Plasma creatinine (1.21 [0.52] vs. 0.90 [0.22] mg/dL, P = 0.066) and UOP (81.5 [31.6] vs. 85.7 [48.9] mL/h, P = 0.795) were not significantly different for samples obtained during the first day of admission for AKI versus non-AKI patients respectively. However, plasma creatinine (1.52 [0.66] vs. 0.83 [0.15] mg/dL,

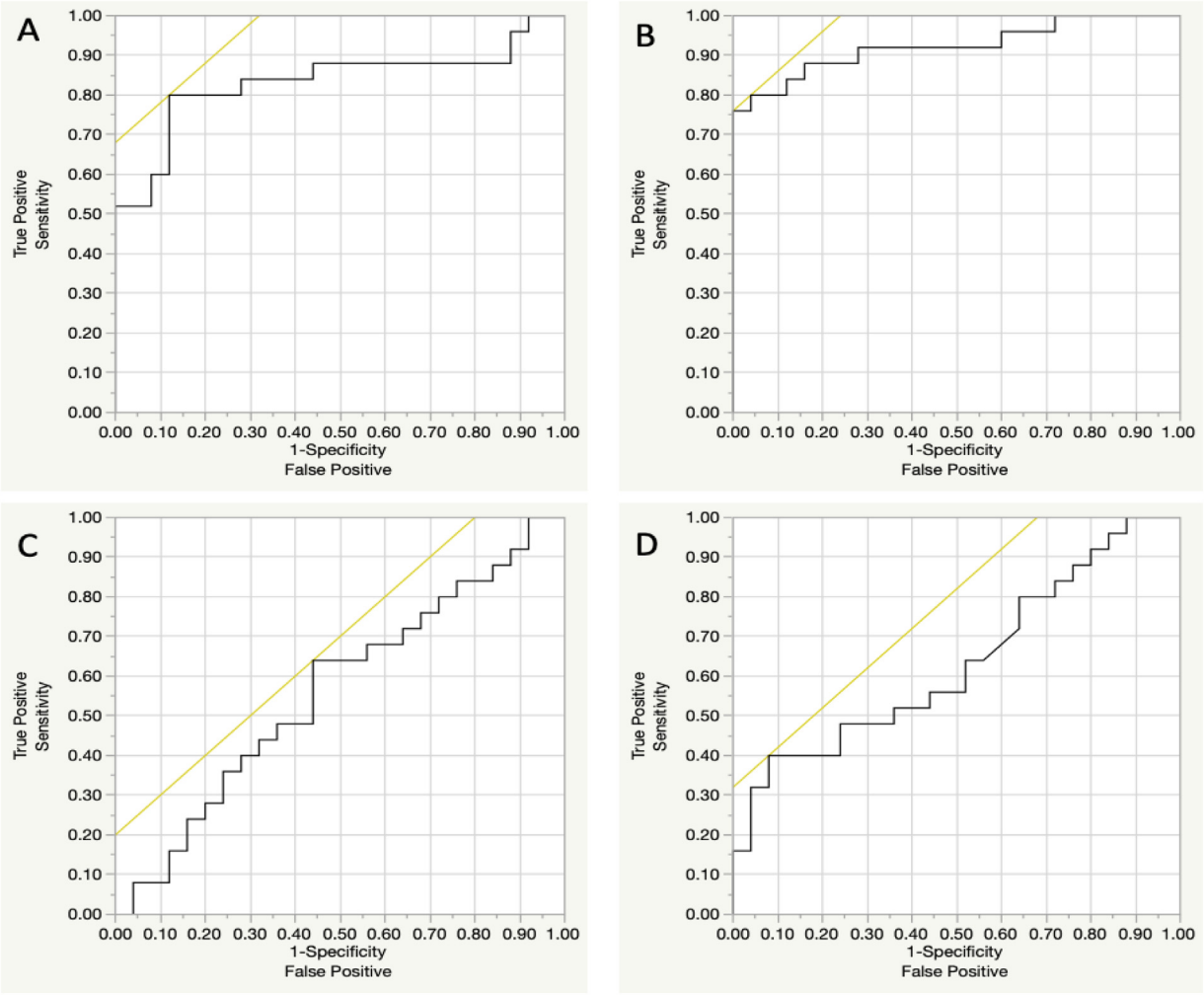

Fig. 2 – Receiver operator characteristic curves for AKI biomarkers.
Panels A–D represent ROC curves for BNP, NGAL, UOP and creatinine respectively. The area under the ROC curves were 0.83, 0.92, 0.56, and 0.64 respectively with NGAL exhibiting the best performance.

P = 0.032) was significantly higher by day two for AKI patients. Based on plasma creatinine and/or UOP values obtained from the EMR, the average time for in the AKI group to achieve at least stage 1 KDIGO criteria was 42.7 (15.8) hours following burn intensive care unit admission. Multivariate logistic regression showed NGAL alone (OR 4.3, 95% CI 1.2–7.5, P = 0.011) to be an independent predictor of AKI when adjusted for age and burn size. The area under the ROC curve showed NGAL providing significantly greater sensitivity and specificity (area under the curve: 0.92) compared to other biomarkers (BNP: 0.83, UOP: 0.56, and creatinine: 0.64) (Fig. 2).

The correlation of the features and their relationship to AKI or No-AKI used in building the *k*-NN ML models is illustrated in the heat map shown in Fig. 3. Using the 80%–20% train–test split of results, we found the *k*-NN algorithm maintained 90% accuracy when including NGAL, creatinine, UOP, and NT-proBNP for *k*-values ranging from 1 to 6, and 8 to 20 (Fig. 4A). When $k = 7$, the accuracy was 100% using the 80%–20% train–test set. With the same train–test split, we found the *k*-NN algorithm to consistently maintain 100% accuracy when excluding NT-proBNP (Fig. 4B). Our cross-validation studies also supported these findings with an average accuracy of 98% (5.4%) when all biomarkers were included. When using only NT-proBNP, UOP and creatinine, accuracy was 80 to 90% (Fig. 4C), which was further supported by our cross-validation study results showing an average accuracy of 88% (14.3%). The UOP and creatinine alone exhibited lowest accuracy ranging from 60 to 80% (Fig. 4D) with a cross validation study results showing an average accuracy of 68% (19.4%).

Similar results were observed using a 60%–40% training–testing split, which showed accuracy ranging from 95 to 100% for *k*-values of 1 to 13 neighbors when NGAL, creatinine, NT-proBNP, and UOP were included. Without NGAL, accuracy decreased from 95 to 60% for $k > 13$. Removing NT-proBNP from the algorithm decreased accuracy from 100 to 70% for *k* values >17. Accuracy varied from 80 to 100% when creatinine was removed from the algorithm across the range of *k*-values. The removal of UOP had the least impact on the ML algorithm with accuracy was maintained at 100% until $k = 15$. When $k > 15$, error rates of 10–35% were observed. Similar to the 80%–20% train–test set analysis of biomarker pairs, we see algorithms using the 60%–40% achieving an accuracy ranging from 90 to 100% when NGAL was included. When creatinine and NT-proBNP were used together and excluding NGAL and UOP, an accuracy ranging from 85 to 90% was achieved for *k*-values ranging from 5 to 13.

The average accuracies obtained from our cross-validation studies for the 2200 ML models for the categories noted above further verified the above trends and results.

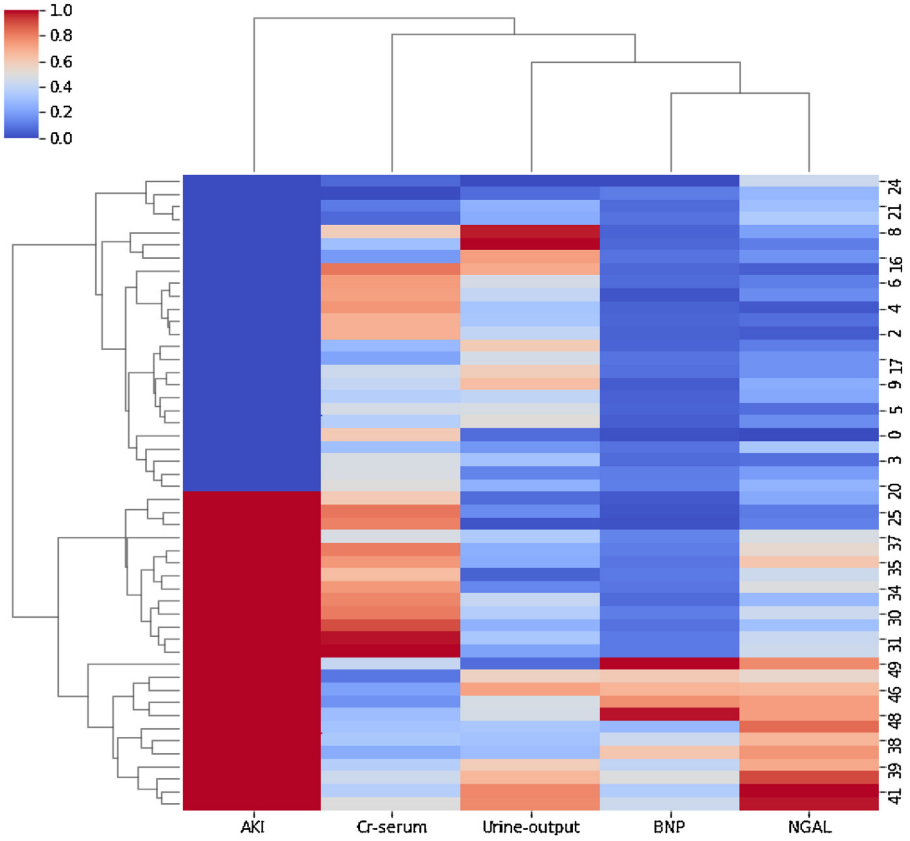

Fig. 3 – Cluster heatmap based on the normalized NGAL, creatinine, NT-proBNP and urine output values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
The heatmap illustrates patients classified as having AKI (red) versus no AKI (blue). Shades of color identifies patients that have abnormally high (red) versus low (blue) values. The x-axis identifies biomarkers and AKI status, while y-axis identifies individual patients (1–50).

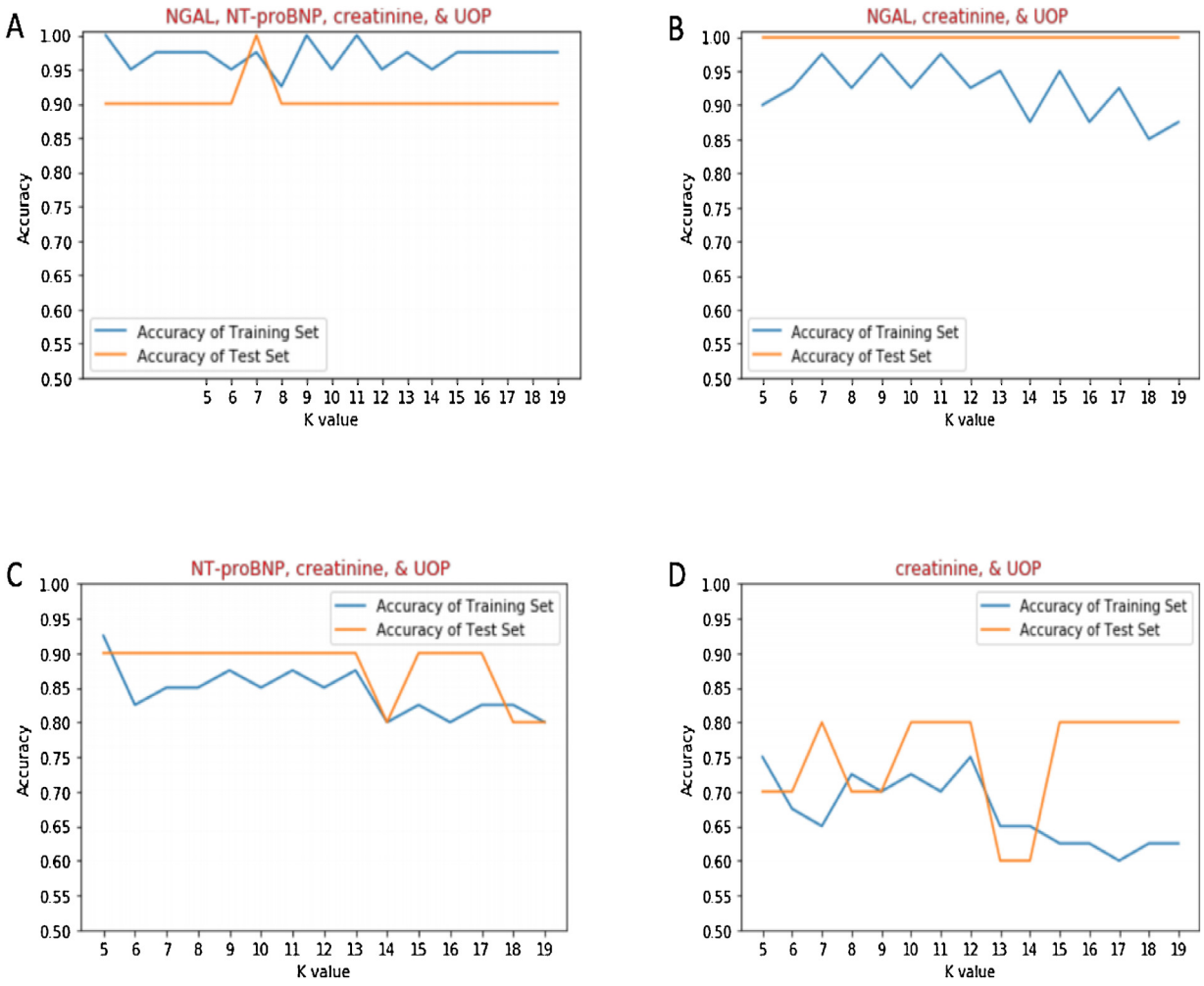

Fig. 4 – k-Nearest neighbor training-testing with NGAL, creatinine, UOP, and NT-proBNP.
The figure illustrates the accuracy versus *k*-value for both training and testing sets (80%–20% training-testing split). Panel A is the *k*-NN model that includes NGAL, NT-proBNP, creatinine, and UOP. Panel B excludes NT-proBNP. Panel C excludes NGAL. Panel D includes only UOP and creatinine.

4. Discussion

This study attempts to utilize AI/ML for burn related AKI. Machine learning in particular offers several advantages over human-based decision making. Advantages include high automation and early classification of subtle changes or patterns via computer-based AKI recognition. Evaluating our burn AKI dataset using a *k*-NN ML algorithm provides a pragmatic and innovative approach that analyzes traditional

Table 3 – Acute kidney injury biomarker tests.

Manufacturer (location)	Platform	Sample type	Format	Analyte(s)
Abbott Laboratories[b] (Franklin Lakes, IL)	Architect	Urine	Mainframe	NGAL
Alere (San Diego, CA)	Triage	Whole blood	POCT	NGAL BNP
Astute Biomedical[a,b] (San Diego, CA)	NephroCheck Test System	Whole blood	POCT	TIMP-2 IGFBP-7
Bioporto Diagnostics[b] (Denmark)	NGAL Test	Urine Plasma	Mainframe	NGAL
Diazyme Laboratory[a,b] (Poway, CA)	Beckman AU Beckman DxC Roche Hitachi Siemens	Plasma Serum	Mainframe	Cystatin C

Abbreviations: BNP, b-type natriuretic peptide; IGFBP-7, insulin-like growth factor binding protein-7; NGAL, neutrophil gelatinase associated lipocalin; POCT, point-of-care testing; TIMP-2, tissue injury metalloprotease-2.
[a] FDA approved.
[b] CE approval.

indicators of renal dysfunction (e.g., creatinine and UOP) as well as novel biomarkers of kidney injury (e.g., NGAL) targeting the critical first 24 h following injury.

In our study, NGAL was shown to be a statistically useful biomarker for predicting AKI on the first day of burn intensive care unit (ICU) admission. These findings support previous studies in this population where statistically significant increases as early as four hours post-admission were predictive of AKI [10,11]. Enhanced predictive performance of NGAL was also reflected with the *k*-NN ML algorithm with classification accuracy approaching 100% even without NT-proBNP and UOP. Unfortunately, NGAL is currently not available in the United States as a Food and Drug Administration approved in vitro diagnostic test, however, several assays are currently in development by multiple manufacturers listed in Table 3.

Urine output has been known to be a poor predictor of AKI especially during acute burn resuscitation [11]. Legrand et al. reported glomerular filtration rate to be altered despite UOP remaining normal due to neurohormonal autoregulation [16]. In fact, the exclusion of UOP appears to enhance performance of our ML algorithm, suggesting UOP creates analytical noise and interfering with the *k*-NN method.

Given that NGAL is not available in the United States, our ML algorithm may serve as a useful supplement for this biomarker especially in the pre-hospital setting where UOP, creatinine and NT-proBNP may be performed at the point of care. Fig. 5 illustrates the conceptual role of an ML algorithm for burn AKI recognition. Our study reinforced the need for careful selection identification of acceptable *k* neighbors (based on the *k* optimizer approach) along with cross validation study to avoid values that could adversely affect the model's accuracy. The feature variations and the two distinct train–test split platforms (80%–20% and 60%–40%) along with the cross-validation studies for the range of *k* values, allowed us build and evaluate over 2200 unique ML models. Both training–testing sets of 60%–40% and 80%–20% provided acceptable balance for classifying burn AKI. The overall trend noted in 60%–40% and 80%–20% train–test split models showed similar patterns with respect to the feature variations (e.g., enhanced accuracy with NGAL and reduced accuracy when using UOP as parameters) which were further supported by our cross-validation results.

Using UOP along with, plasma creatinine, and NT-proBNP in our algorithm, we were able to build some models that were able to achieve up to 90% accuracy within the two train–test split categories (Fig. 4) which could classify new patients as either AKI versus no-AKI within the first 24 h—faster than the average 42.7 (23.2) hours required for these patients to meet KDIGO AKI criteria. With only NT-proBNP and creatinine, the ML algorithm achieved an accuracy ranging from 85 to 90% for samples obtained in the same 24-h time period. Given the widespread availability of creatinine, UOP, and NT-proBNP measurements, our findings suggest ML could serve as a surrogate tool to enhance burn AKI recognition in routine clinical practice and in the absence of NGAL. However, caution is advised when adapting one AI/ML algorithm from one facility to another. Laboratory tests are not created equally and could confound AI/ML applications. For this study, serial creatinine testing post-ICU admission was performed using a different technique at the point of care. Therefore, determining changes between two different creatinine could be confounded by the inherent biological and analytical variability [20–22].

The advent of EMR serves as a double-edged sword. Studies have suggested an average human is unable to integrate more

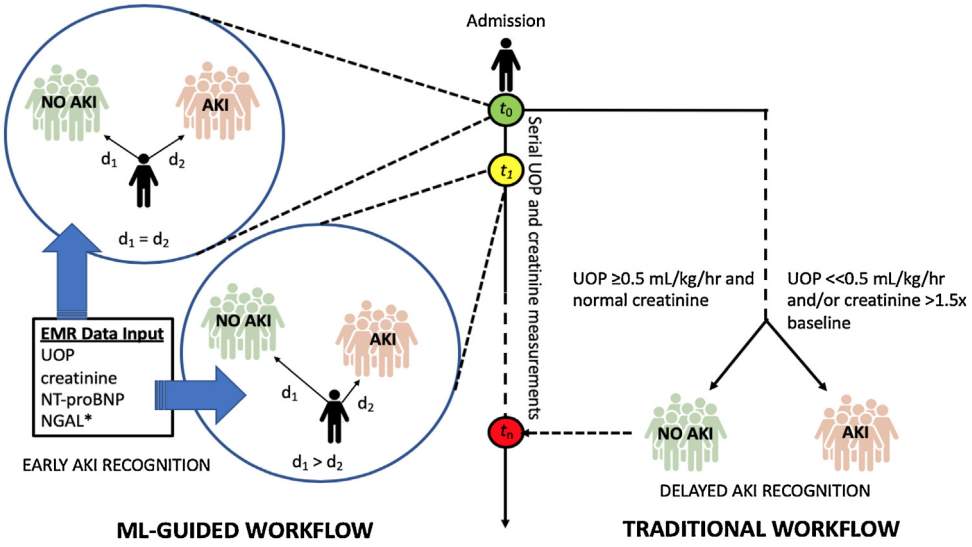

Fig. 5 – Conceptual model for ML-guided burn AKI recognition. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
The figure illustrates a conceptual workflow for ML-guided recognition of burn AKI from time of admission (t_0) to later in the hospital stay (t_n). On the left, EMR data including UOP, creatinine, and NT-proBNP feed into the ML-algorithm. At admission, there is insufficient data to cluster into the AKI (orange) versus no AKI (green) group, and thus, the distance between these two groups are similar ($d_1 = d_2$). As sufficient data becomes available, the clustering distance (d_2) decreases towards the AKI population. The asterisk (*) denotes NGAL as an optional biomarker. For the traditional workflow on the right, late recognition occurs due to delayed identification of changes in UOP and/or creatinine based on KDIGO criteria.

than seven pieces of information at any given time [23]. In part, EMR systems have provided means to capture and organize the substantial volumes of medical information [24,25]. However, as the number of laboratory tests grow [26] along other health information, the EMR becomes overwhelming for providers and prevents conversion of these data into timely and clinically actionable knowledge. Artificial intelligence overcomes these human limitations. With advances in portable computing power, AI/ML may be employed as part of EMR decision support and/or handheld smart devices to augment decision making at the bedside. For our study, AI/ML has shown clinical utility for burn-related AKI when using just a few routine laboratory results.

Limitations of the study include having a modest sample size and the retrospective nature of the analysis. The intent of the study was to train and validate an *k*-NN-based ML algorithm to determine clinical utility for burn AKI recognition within the critical initial 24 h following burn ICU admission. Neutrophil gelatinase associated lipocalin was selected due to its previous performance in burn patients, availability as a central laboratory test, and the clinical demand at our institution over other commercially available biomarkers (i.e., TIMP-2 and IGFBP-7). Lastly, the classification of AKI remains based on clinically accepted consensus guidelines (i.e., KDIGO). The performance of any AI/ML platform would be influenced by a priori classification methods.

5. Conclusion

Burn patients are at high risk for AKI. Machine learning using *k*-NN techniques augments predictive classification of AKI in severely burned patients within the first 24 h of admission. Our ML algorithm was heavily weighted by NGAL measurements. Unfortunately, given the limited availability of NGAL as well as other FDA approved AKI biomarkers in the United States, alternative approaches are needed to enhance recognition of burn patients with AKI. Using common laboratory measurements such as creatinine, UOP, and NT-proBNP, our ML algorithm provided reasonable accuracy and identified AKI patients earlier than the UOP- and creatinine-based KDIGO criteria—suggesting ML could augment the performance of traditional AKI biomarkers in the burn population. Future prospective observational studies are needed to determine the clinical impact of ML-assisted AKI recognition in burn patients, as well as evaluate the significance of different laboratory methods for AI/ML diagnostic applications.

Declarations of interest

None.

Acknowledgements

We thank clinical laboratory scientists supporting the NGAL testing and research specialists for collecting study data. The study was supported in part by an intramural Medicine-Surgery-Pathology grant, and as part of a hospital quality project.

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