Iowa Initiative for Artificial Intelligence
Final Report

Project title:	Reducing Nephrotoxic Medication-Associated Acute Kidney Injury in Adults
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Were specific aims fulfilled:	Yes
Readiness for extramural proposal?	Yes x 2
If yes … Planned submission date	July 2023, September 2023
Funding agency	NIH and VHA
Grant mechanism	K23 and CDA
If no … Why not? What went wrong?	N/A

Brief summary of accomplished results:

Research report:

Aims (provided by PI):

Acute kidney injury (AKI) is an abrupt decrease in kidney function that occurs in 20-25% of hospitalized adults, and even "mild" AKI is associated with dramatic increases in both short- and long-term rates of chronic kidney disease, end-stage kidney disease, cardiovascular disease, and death. One major contributor to AKI development is the use of nephrotoxic medication (NTMx), which may complicate as many as one quarter of all AKI episodes. NTMx-AKI is therefore a highly relevant health care issue that impacts large numbers of patients; however, NTMx-AKI is also very difficult to study due to multiple analytical challenges including debate over which medications should be classified as nephrotoxins, confounding related to complex medication regimens in the hospital, and confounding due to the underlying illness being treated.

Notably, there are few effective treatments once AKI has occurred, and so a great deal of focus has been on prevention. The University of Iowa Stead Family Children's Hospital is one of a handful of hospitals across the country using Nephrotoxic Injury Negated by Just-in-Time Action (NINJA), a program designed to identify pediatric patients with high exposure to NTMx and subsequently to reduce NTMx burden and lower rates of AKI. Our preliminary data suggests this program is likely to be effective in the adult population as well. However, in order to successfully transition this program into the adult population, which is quite different from the pediatric population in terms of underlying illnesses, comorbidities, and medication burden, it is critical that the definition of high NTMx burden be optimized for the adult population.

In this proposal, we aim to use hospital data available through the EPIC electronic medical record (EMR) including patient demographic data, patient comorbidities, inpatient laboratory values, vital signs, admission diagnosis, and illness severity in combination with artificial intelligence and machine learning (AI/ML) methods to determine which medications are most nephrotoxic, which medication combinations increase nephrotoxicity, and which patients are at highest risk for NTMx-AKI. These aims will be foundational step to to future R-level proposals to reduce use of NTMx in high-risk patients, thereby reducing rates of AKI and improving short- and long-term patient morbidity and mortality. The following specific aims will be pursued:

Aim 1: Use AI/ML techniques and EPIC EMR data to determine which medications and combinations of medications are most nephrotoxic in the inpatient hospital setting accounting for patient demographics, comorbidities, and underlying disease processes. Hypothesis: We will be able to use readily-available and reliable EPIC EMR variables to determine the medications and combinations of medications that most increase a patient's risk of developing AKI while hospitalized. Inputs will include readily-available and reliable patient data and medication administration records, and output will be the development of AKI related to NTMx use, defined using reliably available creatinine laboratory data.

Aim 2: Develop and optimize prediction models to identify patients with a significant NTMx burden who are at high risk to develop AKI within 48 hours and 72 hours. Hypothesis: We will be able to use the definitions of NTMx burden to identify patients at high risk of AKI development within 48 hours and 72 hours.

Successful completion of these Aims will significantly increase our understanding of nephrotoxicity in the adult population, and will position us for future projects to refine our ability to identify at-risk patients with high NTMx burdens in real time, with the ultimate goal of a large-scale trial to demonstrate the effectiveness of using a program in adults to reduce exposure to NTMx in high-risk patients and prevent AKI development.

Data for Aims:

The study population for this retrospective cohort analysis consisted of adult patients aged 18 years and older who were admitted to the University of Iowa Hospital between 2017 and 2022. To be eligible for inclusion, patients needed to have at least one patient-day of exposure to high-nephrotoxin medications. The study received approval from the local institutional review board (HawkIRB 202008447).

Exclusion criteria were applied to ensure the quality and relevance of the data. Patients were excluded if they met any of the following criteria:

- Admissions lasting less than 48 hours.
- Patients with a baseline estimated glomerular filtration rate (eGFR) less than 15 mL/min or patients on dialysis before admission.
- Patients with Acute Kidney Injury (AKI) already present at the time of admission.
- Patients with fewer than two creatinine values recorded during the admission.
- Absence of a complete blood count (CBC) laboratory test during hospitalization.
- Missing demographic data, including age at admission, race, and sex.
- Missing comorbidity data.
- Absence of vital sign data during admission.

The study defined high-nephrotoxin exposure using the NINJA program, identifying patients who received three or more nephrotoxic medications in one day or intravenous aminoglycoside or vancomycin for three or more days. Specific medications like iodinated contrast dye, liposomal amphotericin, and cidofovir were considered administered for six days following actual use.

AKI diagnosis followed KDIGO guidelines, requiring a creatinine increase of at least 0.3 mg/dL from baseline. Baseline creatinine levels were the lowest within six months before or at admission.

The machine learning algorithm development incorporated demographic data, patient co-morbidities, daily laboratory values, vital signs, admitting service, and medication records for 57 nephrotoxic medications. These variables were used to train models for AKI prediction.

After the preprocessing step, the data includes 248698 hospital days with 16295 hospital admissions for analysis of Aim 1 and Aim2.

AI/ML Approach:

In this section, we outline the methodology employed for our analysis, which focuses on predicting Acute Kidney Injury (AKI) in patients. We utilized two distinct neural network architectures, the Recurrent Neural Network

(RNN) with Gated Recurrent Units (GRUs) for AIM 2 and the Artificial Neural Network (ANN) for AIM 1. This selection was made based on their suitability for handling sequential data and complex patterns within our dataset.

Data Pre-processing:

Data Pre-processing for Factor Importance Analysis(AIM1):

- Transformed longitudinal data from each unique admission into a single row.
- Separated laboratory values and vital signs into highest and lowest values during hospitalization.
- Excluded patients with missing demographic or comorbidity data or without laboratory/vital sign information.
- Required at least one patient-day to meet the high nephrotoxin exposure criteria for inclusion based on NINJA criteria.

Data Pre-processing for Time-Series Analysis(AIM2):

- Excluded patients with missing demographic or comorbidity information and those lacking laboratory or vital sign data.
- For patient-days without laboratory or vital sign values, filled gaps by forward-filling and then backward-filling.
- In cases of multiple values on patient-days, selected the median value, except for mean arterial pressure (MAP), which recorded both maximum and minimum values separately.
- Removed admissions with the lowest creatinine value below 0.4 or above 4.
- Excluded hospitalizations with less than 5 days of patient-days per visit.

Model design:

Model Design for AIM 1:

For AIM 1, an Artificial Neural Network (ANN) model is employed. This choice of architecture is motivated by the need to analyze a wide range of patient data and medication records to identify nephrotoxic medications while considering patient demographics and comorbidities.

The ANN model consists of two dense layers sandwiched between Batch Normalization and Dropout layers. The use of Batch Normalization helps stabilize and accelerate training by normalizing the inputs between layers. The Dropout layers, with a 50% dropout rate, serve to prevent overfitting, ensuring that the model generalizes well to unseen data.

The activation function used within the dense layers is Rectified Linear Unit (ReLU). ReLU is known for its efficiency in capturing nonlinear relationships in data, making it suitable for this complex task. In the final output layer, a sigmoid activation function is applied for binary classification, allowing the model to distinguish between patients at risk of developing AKI due to nephrotoxic medication use and those who are not.

To enhance the model's generalization capabilities and reduce the risk of overfitting, L1 and L2 regularization with strengths set at 0.01 are applied. This regularization helps the model focus on important features and prevents it from becoming overly complex.

A learning rate of 0.001 is employed to optimize the model's performance during training. This careful selection of hyperparameters, along with the choice of activation functions and regularization techniques, ensures that the model effectively analyzes patient data and medication records to identify the most nephrotoxic medications.

Model Design for AIM 2:

For AIM 2, a Gated Recurrent Unit (GRU) model is chosen. The GRU model is well-suited for handling sequential data and capturing temporal dependencies, making it ideal for predicting AKI development within a critical 48-hour window while considering the burden of nephrotoxic medications (NTMx).

The GRU model is structured with three GRU layers, each with varying units (64, 32, and 16). This layering strategy is designed to capture different levels of temporal dependencies in the data. It allows the model to understand how NTMx exposure evolves over time, which is crucial for identifying patients at high risk of AKI development.

To prevent overfitting and enhance model robustness, Batch Normalization and Dropout layers are interspersed with a 25% dropout rate. These layers ensure that the model does not rely on noisy or irrelevant patterns in the data.

The final output layer employs a sigmoid activation function for binary classification, distinguishing between patients at high risk of AKI development within 48 hours and those who are not. L1 and L2 regularization strengths are set at 0.01 to further reduce the risk of overfitting, ensuring that the model's predictions are reliable.

A learning rate of 0.0001 is used for fine-tuning the model. This choice of hyperparameters and model architecture enables the GRU model to effectively capture temporal patterns in NTMx exposure and predict AKI development within a critical timeframe.

In summary, the ANN model for AIM 1 and the GRU model for AIM 2 are selected based on their suitability for handling complex patient data and sequential information, respectively. These models are designed with careful consideration of hyperparameters and regularization techniques to ensure accurate and reliable predictions for nephrotoxicity and AKI risk.

Experimental methods, validation approach:

The train: test split is 80:20.
AIM1 Network:

```
Model: "model"
_________________________________________________________________
 Layer (type)                Output Shape              Param #
=================================================================
 input_1 (InputLayer)        [(None, 91)]              0

 dense (Dense)               (None, 256)               23552

 batch_normalization (BatchN  (None, 256)              1024
 ormalization)

 dense_1 (Dense)             (None, 128)               32896

 batch_normalization_1 (Batc  (None, 128)              512
 hNormalization)

 dropout_1 (Dropout)         (None, 128)               0

 dense_2 (Dense)             (None, 1)                 129

=================================================================
Total params: 58,113
Trainable params: 57,345
Non-trainable params: 768
_________________________________________________________________
```

Aim2 network:

```
Model: "sequential"
_________________________________________________________________
 Layer (type)                Output Shape              Param #
=================================================================
 gru (GRU)                   (None, 4, 64)             30912

 batch_normalization (Batch  (None, 4, 64)             256
 Normalization)

 dropout (Dropout)           (None, 4, 64)             0

 gru_1 (GRU)                 (None, 4, 32)             9408

 batch_normalization_1 (Bat  (None, 4, 32)             128
 chNormalization)

 dropout_1 (Dropout)         (None, 4, 32)             0

 gru_2 (GRU)                 (None, 16)                2400

 batch_normalization_2 (Bat  (None, 16)                64
 chNormalization)

 dropout_2 (Dropout)         (None, 16)                0

 dense (Dense)               (None, 16)                272

 dropout_3 (Dropout)         (None, 16)                0

 dense_1 (Dense)             (None, 2)                 34

=================================================================
Total params: 43474 (169.82 KB)
Trainable params: 43250 (168.95 KB)
Non-trainable params: 224 (896.00 Byte)
_________________________________________________________________
```

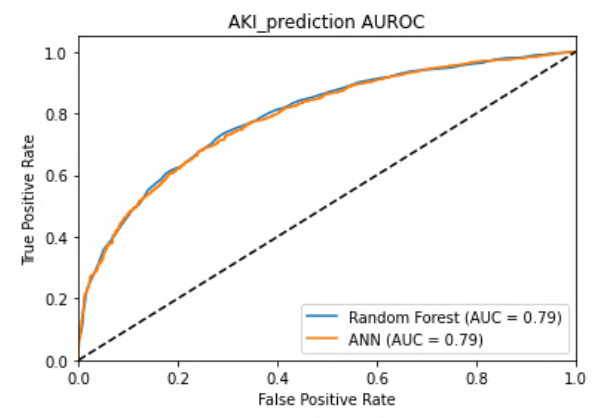
We used Adam with following configuration:
Aim1= learning_rate=1e-3, decay= 1e-5
Aim2= learning_rate=1e-4, decay= 1e-5

Binary_crossentropy loss for both aims.

All the models are trained for 200 epochs with 256 as batch size.

Results:

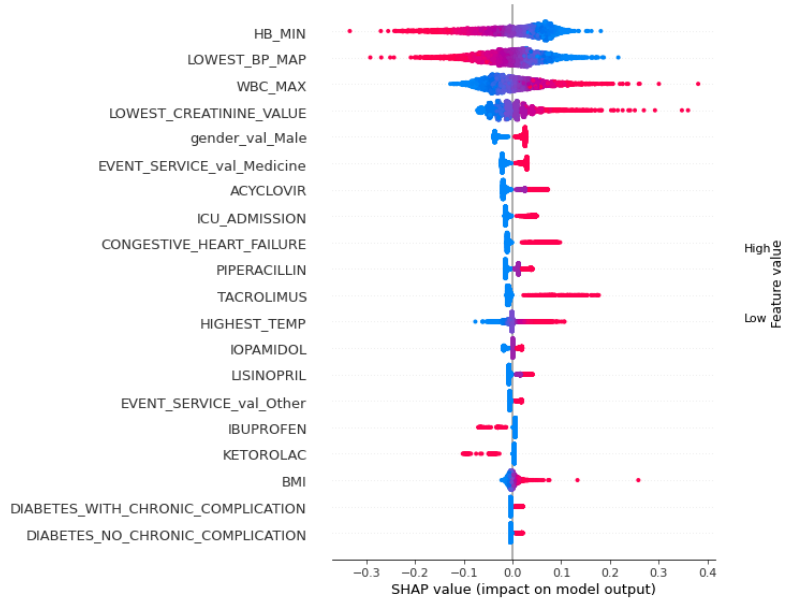
The results for the model are as follows.
Aim1:

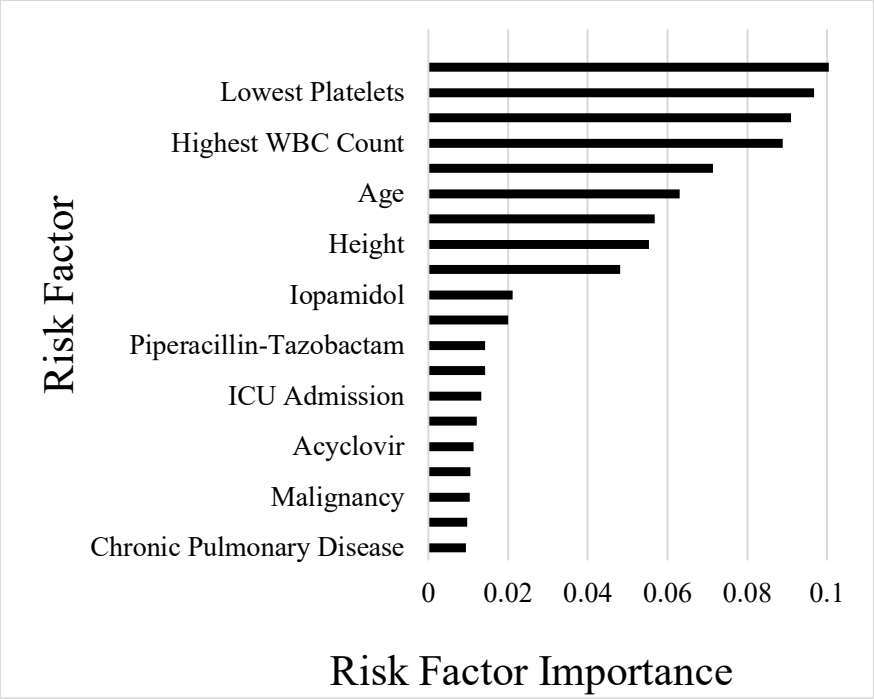


ANN Model:
F1 Score: 0.8164406646196773
AUROC: 0.7884904063456051

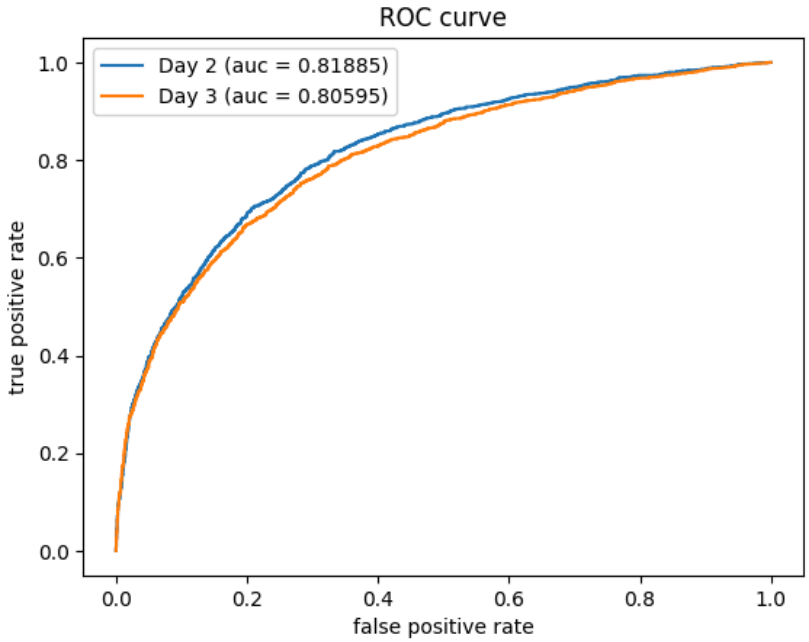
	precision	recall	f1-score	support
0.0	0.65	0.47	0.54	1089
1.0	0.77	0.87	0.82	2171
accuracy			0.74	3260
macro avg	0.71	0.67	0.68	3260
weighted avg	0.73	0.74	0.73	3260

Confusion Matrix:
[[510 579]
 [274 1897]]




Lowest Platelets
Highest WBC Count
Age
Height
Iopamidol
Piperacillin-Tazobactam
ICU Admission
Acyclovir
Malignancy
Chronic Pulmonary Disease
Risk Factor
0
0.02
0.04
0.06
0.08
0.1
Risk Factor Importance

Aim2:


ROC curve
Day 2 (auc = 0.81885)
Day 3 (auc = 0.80595)
true positive rate
false positive rate
0.0
0.2
0.4
0.6
0.8
1.0

```
Label 0
Confusion Matrix:
[[[1027  564]
  [ 678 3286]]

 [[3286  678]
  [ 564 1027]]]
Classification Report:
              precision    recall  f1-score   support

         0.0       0.85      0.83      0.84      3964
         1.0       0.60      0.65      0.62      1591

    accuracy                           0.78      5555
   macro avg       0.73      0.74      0.73      5555
weighted avg       0.78      0.78      0.78      5555

Label 1
Confusion Matrix:
[[[1279  496]
  [ 971 2809]]

 [[2809  971]
  [ 496 1279]]]
Classification Report:
              precision    recall  f1-score   support

         0.0       0.85      0.74      0.79      3780
         1.0       0.57      0.72      0.64      1775

    accuracy                           0.74      5555
   macro avg       0.71      0.73      0.71      5555
weighted avg       0.76      0.74      0.74      5555
```

In the Above figure Label 0 corresponds to Day2 and Label 1 corresponds to Day 3

Main Findings:

- A Recurrent Neural Network (RNN) with Gated Recurrent Unit (GRU) machine learning model was applied to predict Acute Kidney Injury (AKI) following high nephrotoxin exposure in adult inpatients.
- The RNN-GRU model achieved a higher positive predictive value without a significant reduction in AKI case identification compared to previous methods.
- An Artificial Neural Network (ANN) was used to identify key risk factors in AKI prediction, highlighting the importance of laboratory data, vital signs, and specific medications.
- Key medications associated with AKI risk included iopamidol, vancomycin, piperacillin-tazobactam, and lisinopril.
- Factors like BMI and height were also found to be important predictors of AKI, particularly in patients with higher BMI.
- The RNN-GRU model's accuracy was significantly improved by incorporating clinical data, suggesting potential enhancements to AKI prevention programs like NINJA.
- The study addresses limitations in current AKI alert systems by focusing on prevention and real-time communication between healthcare teams.

- The RNN algorithm substantially reduces false alerts for nephrotoxic AKI in adults, making NINJA implementation in adult hospitals more feasible and resource-efficient.

- Limitations include the possibility of missing important clinical characteristics or medications, the need for validation in different populations, and differences in outcomes between the RNN-GRU and ANN models.

In conclusion, the RNN-GRU machine learning model enhances AKI prediction and facilitates targeted intervention with fewer false alerts, potentially improving patient outcomes in the adult population.

Ideas/aims for future extramural project:

In our K23 grant application, our proposal focuses on incorporating our findings into a real-time EMR alert for patients at high-risk to develop nephrotoxic AKI, linked to a robust action plan featuring input from pharmacists, nephrologists, and the primary team to appropriately modify nephrotoxic regimens prior to AKI development.

In our CDA proposal, we will use the results of this project to identify patients at high risk to develop AKI. This enriched population will be enrolled in a study looking the utility of novel AKI biomarkers to identify patients with structural injury rather than hemodynamic injury, and short- and long-term outcomes between these groups will be compared.