Development and Validation of a Tool to Predict Short Term Opioid Overdose Risk After Acquiring a Prescribed Controlled Substance

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BACKGROUND

- Despite decreased in opioid prescribing over the last decade, Opioid Overdoses (OOD) continue rise with over 10,000 fatal opioid overdoses are attributed to prescription opioids annually.[1]
- Our team recently discovered a strong temporal association between controlled substance (CS) acquisition and OOD, with CS acquisition in the 7 days prior to OOD nearly doubling the risk of OOD compared to CS acquisition weeks to months prior to OOD.[2, 3]
- Most OOD risk prediction tools published in the literature ascribe risk cumulatively over fixed time windows rather than focus on near-term OOD risk.[4]

Objective: To develop an opioid overdose (OOD) risk prediction tool that is specifically aimed at predicting OOD risk in the near term (7 and 30 days) after acquiring prescribed controlled substances (CS).

METHODS

Data Sources: This study utilized linked Arkansas statewide data between January 1st, 2014 and December 31st, 2020. CS acquisition was assessed using Arkansas Prescription Drug Monitoring Program (AR-PDMP) data which were probabilistically linked, at the patient level, to statewide death certificate, inpatient discharge, and emergency department data to identify fatal and non-fatal OOD. After the data were linked, all patient identifiers were destroyed resulting in a de-identified data source that was determined not to be human subjects research.

Study Sample:

- Individuals who acquired ≥1 CS prescription(s) were included in the analysis.
- Persons with in-valid ages (age<0 or age >120) were excluded.
- Unit of analysis was each day's worth of prescription CS acquisitions for every identified individual.

Study Measures: Features engineered on each CS dispensing date included patient demographics, characteristics of opioids dispensed, characteristics of other controlled substances dispensed, number of unique prescribers/pharmacies, and measures of prior OOD.

Statistical Analysis:

- The data were randomly split 1:1 into training and test sets.
- A 1:100 random undersampling (RUS) of the majority class was performed to address severe data imbalance (<0.01% minority class).
- Stepwise regression was used to reduce feature space.
- Hyperparameter tuning was performed using RandomizedSearchCV from the scikit-learn library in Python to further enhance the performance of machine learning models.
- 10-fold cross validation was conducted to mitigate overfitting risks.
- Model discrimination was assessed on the full test set using c-statistics, AUC-ROC curves and confusion matrices.
- The performance of multiple machine learning algorithms, including random forest, logistic regression, naïve bayes, and gradient boosting were compared.

RESULTS

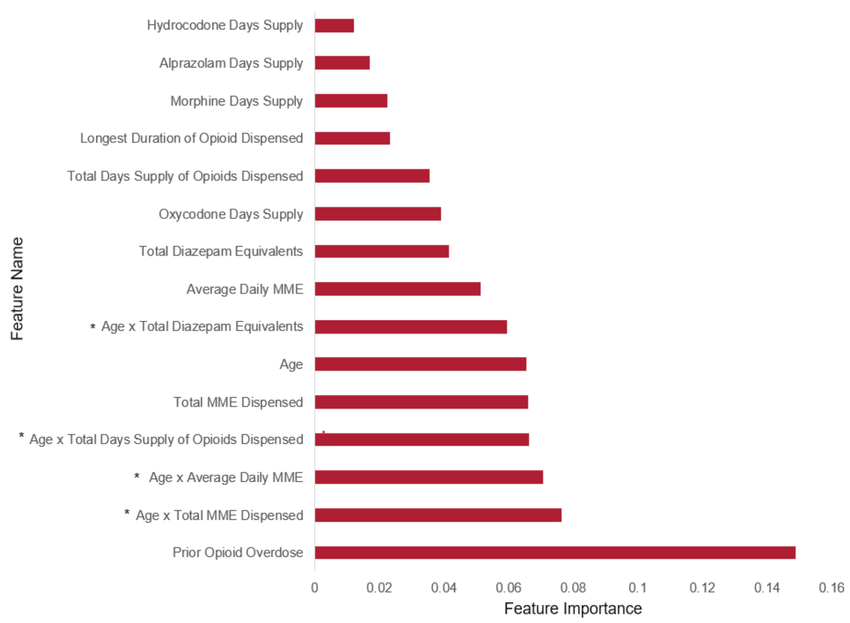
- A total of 2,818,135 persons filled at least one controlled substance during the study period, 8,436 of which experienced one or more OODs.
- The models trained using the random forest classifier had the highest discrimination in predicting OOD in the 7 and 30 days following CS acquisition

Model Performance for Opioid Overdose Prediction within 7 and 30 days Following Prescription Controlled Substance Acquisition

Within 7 days					
Classifier	**AUC-ROC (c-statistic)**	**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**
Random Forest	0.773	62.44%	77.40%	0.02%	100.00%
Logistic Regression	0.767	61.21%	76.42%	0.02%	100.00%
Naïve Bayes	0.735	50.35%	84.15%	0.03%	100.00%
Gradient Boosting	0.769	56.58%	81.74%	0.02%	100.00%
Within 30 days					
Classifier	**AUC-ROC (c-statistic)**	**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**
Random Forest	0.751	62.43%	73.41%	0.06%	99.99%
Logistic Regression	0.747	66.17%	68.61%	0.06%	99.99%
Naïve Bayes	0.727	45.50%	85.95%	0.09%	99.98%
Gradient Boosting	0.747	58.08%	77.32%	0.07%	99.99%

AUC = Area Under the Receiver Operating Characteristic Curve

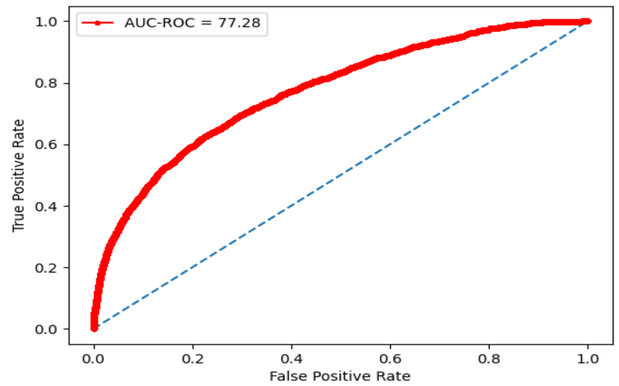
Random Forest Feature Importance for Prediction of Opioid Overdose within 7 days Following Prescription Controlled Substance Acquisition



MME = Morphine Milligram Equivalents

*Age was interacted with several features with high feature importance to enhance the performance of models trained with the logistic regression classifier

Prediction of Opioid Overdose within 7 days Following Prescription Controlled Substance Acquisition: Area Under the Receiver Operating Characteristic (AUC-ROC) Curve for the Random Forest Trained Model



AUC = Area Under the Receiver Operating Characteristic Curve

Prediction of Opioid Overdose within 7 days Following Prescription Controlled Substance Acquisition: Confusion Matrix for the Random Forest Trained Model

		Predicted		
		OOD*	No OOD*	Row Total
Actual	OOD*	1,172	705	1,877
	No OOD*	5,190,221	17,776,330	22,966,551
	Column Total	5,191,393	17,777,035	

OOD = Opioid Overdose

*Opioid overdose within 7 days following prescription controlled substance acquisition

CONCLUSION

- ✓ **Despite only a limited range of features derived almost exclusively from AR-PDMP records, good model discrimination was still achieved for the prediction of OOD immediately following CS prescription acquisition.**
- ✓ **This tool has potentially clinical utility for identifying patients at high-risk for OOD in the near-term following receipt of a prescription CS.**

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