A Machine Learning-Based Diagnostic Utility for Predicting Ertapenem Resistance in Klebsiella Pneumoniae Using MALDI-TOF MS Spectra

A novel diagnostic approach combining MALDI-TOF mass spectrometry with lightweight machine learning models for rapid antimicrobial resistance detection in clinical settings.

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Agenda

Problem Statement

Global Health Threat

Klebsiella pneumoniae (K. pneumoniae) causes over **600,000 deaths annually** worldwide and accounts for nearly one-third of all gram-negative bacterial infections.

Hospital-acquired infections from this pathogen represent 3-8% of cases in the United States, with pneumonia mortality rates reaching **50%**.

Carbapenem Resistance in K. pneumoniae

Carbapenem is a class of last-resort antibiotics used for treating K. pneumoniae. Bacterial strains resistant to it pose severe treatment challenges, making clinical options **extremely limited**. Ertapenem (member of the carbapenem class) resistance serves as an early warning signal for broader carbapenem resistance, making rapid detection essential for patient outcomes.

Traditional Detection Methods

Before advanced techniques, identifying antibiotic resistance relied on established, but often time-consuming, laboratory procedures.

Culture-Based Testing

Time-consuming: Requires ~ **24-72 hours** for results.

Labor-intensive: Demands significant manual effort and personnel.

Molecular Methods (PCR and Whole-Genome Sequencing)

Higher costs: Involves expensive reagents and consumables.

Specialized equipment: Limits broad clinical application due to infrastructure needs.

MALDI-TOF MS: A Rapid Alternative

Revolutionary Technology

Instant Identification

Identifies bacterial species within minutes, requiring minimal sample preparation.

Efficient & Reliable

Generates protein-based spectral profiles for high throughput, offering speed and reproducibility.

The Gap We Address

While Matrix-Assisted Laser Desorption/Ionization - Time-Of-Flight Mass Spectrometry (MALDI-TOF MS) excels at species identification, determining antibiotic resistance still requires additional time-consuming manual processes. Our research uses **machine learning algorithms to automate this critical gap**.

What Makes our Research Unique

Species-Specific Focus

Unlike generic approaches, we target **Klebsiella pneumoniae** exclusively, improving prediction accuracy for this critical pathogen.

Ertapenem-Centered

We focus on **ertapenem** as a resistance marker because it's cost-effective, easy to administer, and signals emerging broader carbapenem resistance.

Lightweight Models

Our approach uses **lightweight machine learning algorithms** that run on standard computers, making deployment realistic for everyday clinical workflows.

The DRIAMS Dataset

300K+ samples

4 medical institutes

6,000 features

3 Dalton Intervals

The **Database of Resistance Information on Antimicrobials and MALDI-TOF Mass Spectra (DRIAMS)** dataset provides comprehensive clinical data from Swiss medical institutes, including microbiological information and detailed antibiotic susceptibility profiles. It processes MALDI-TOF MS spectra using the binned 6000 format.
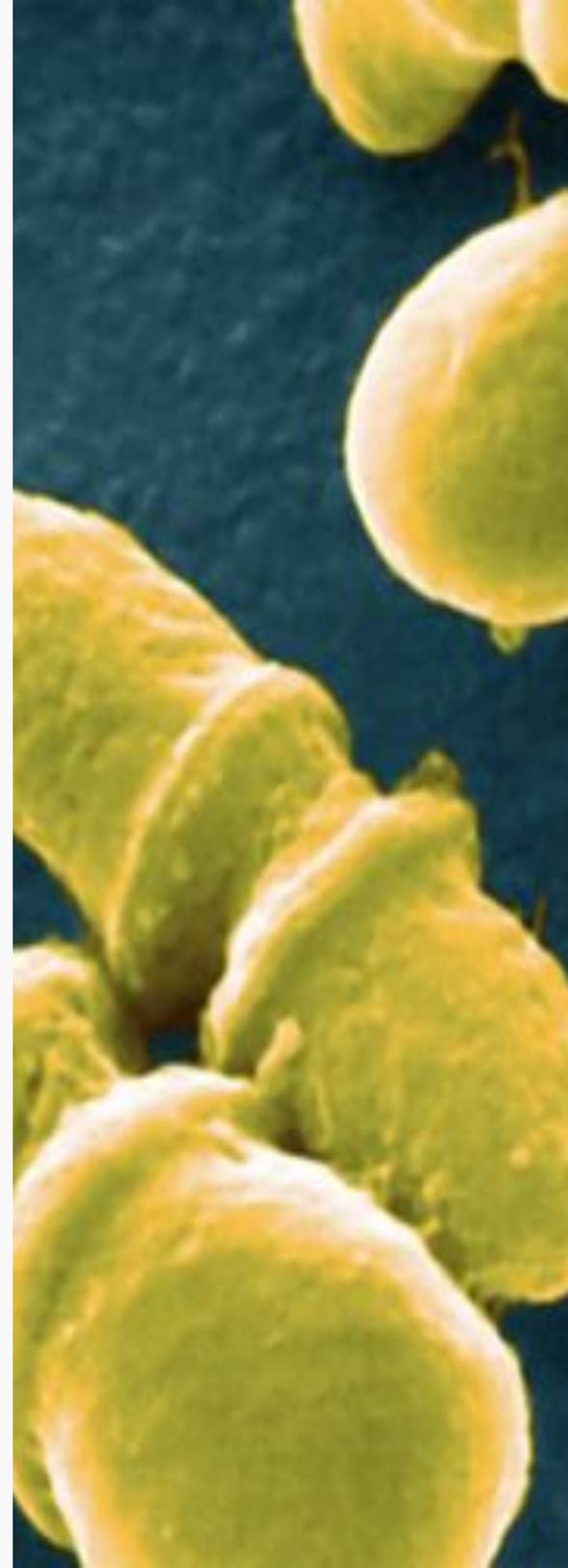
End-to-End Methodology

Data Extraction

Filtered for Klebsiella pneumoniae isolates, extracted spectral data, and classified resistance labels as susceptible, resistant, or uncertain.

Preprocessing

Applied log-based variance stabilization, aligned spectra, and removed noise to ensure data quality and feature consistency.

Feature Selection

Used Recursive Feature Elimination (RFE) to reduce 6,000 features to 96 most informative bins distinguishing resistant from susceptible isolates.

Model Training & Testing

Evaluated and tested four ML algorithms (Logistic Regression, KNN, MLP, Random Forest) with stratified 80-20 train-test split and hyperparameter tuning using cross-validation. Relied on metrics such as Accuracy, Precision, Recall, and F1-Score, as well as normalized Confusion Matrices.

Four Machine Learning Models

Logistic Regression

Logistic Regression estimates resistance probability using linear relationships in spectral features, with the regularization strength tuned across values from 0.01 to 100 and sufficient iterations used to ensure convergence.

K-Nearest Neighbors (KNN)

The KNN model classifies samples by majority vote among the k nearest neighbors in feature space, with neighbor values from 1 to 15 evaluated to identify the most effective local similarity patterns.

Multi-Layer Perceptron (MLP)

The MLP learns nonlinear patterns in spectral data, with learning rates from 0.000001 to 0.05 and training epochs from 10 to 100 tuned for best convergence.

Random Forest

The Random Forest model combines multiple decision trees to improve robustness, with tree depths from 1 to 7 and estimator counts from 10 to 100 explored to balance model complexity and accuracy.

Addressing Class Imbalance

5,069 Susceptible Isolates

Overwhelming Majority

94 Resistant Isolates

Critically underrepresented

17 Uncertain Isolates

Minority group

Performance Comparison of Balancing Strategies

Technique	Accuracy	Precision (Macro/Avg)	Recall (Macro/Avg)	F1-Score (Macro/Avg)	False Negative Rate
Undersampling	**0.86**	**0.81/0.86**	**0.82/0.86**	**0.81/0.86**	**26.32%**
SMOTE	0.95	0.62/0.98	0.82/0.95	0.66/0.96	68.42%
ADASYN	0.95	0.68/0.98	0.79/0.95	0.64/0.96	36.84%
Class-Weighting	0.99	0.99/0.99	0.63/0.99	0.70/0.98	73.68%

Why Undersampling Was Selected Despite Lower Accuracy

While SMOTE, ADASYN, and Class Weighting showed higher overall accuracy, they yielded significantly worse precision and recall (macro) scores. Most critically, these methods resulted in very high false negative rates, meaning they frequently failed to detect antibiotic-resistant cases. In a clinical context, false negatives are dangerous as they can lead to inappropriate treatment. Undersampling achieved the best balance with a significantly lower false negative rate and improved precision/recall, making it the most clinically safe choice. A slightly lower overall accuracy is acceptable when it means fewer missed resistant cases.

Model Training Results

The following charts illustrate the training performance of each machine learning model, showcasing their strengths and areas for optimization on the training dataset. We carefully analyzed key metrics for each to understand their behavior before testing on unseen data. Based on overall accuracy and stability during training, Logistic Regression, Random Forest, and MLP were selected for final evaluation on the test dataset.
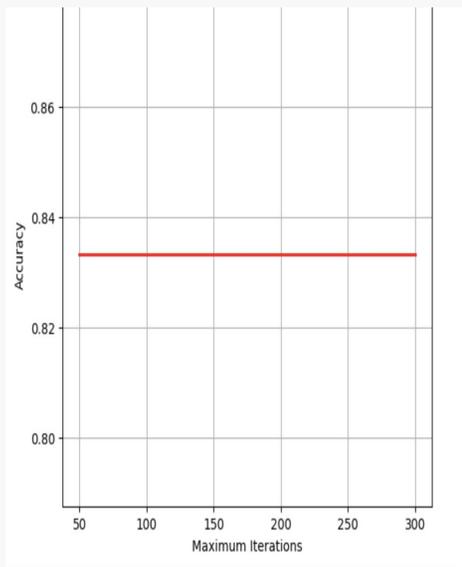

Logistic Regression: 83% Accuracy

Logistic Regression maintained a constant training accuracy of 83% across different maximum iteration values, indicating that iteration count did not affect model performance.
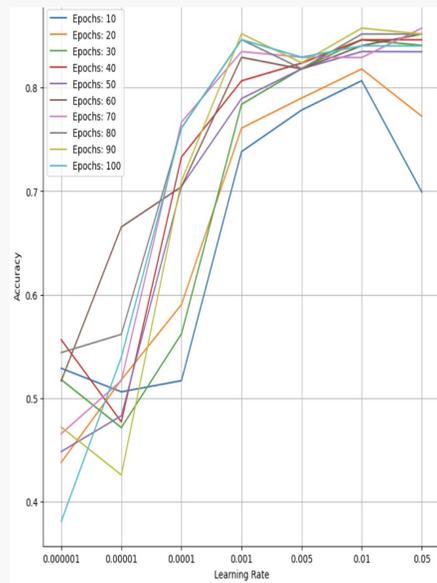
MLP: 85.7% accuracy

The MLP accuracy varies with learning rate and epochs, and the results show that a learning rate of 0.01 with 90 epochs gives the most stable performance, achieving 85.7% accuracy.
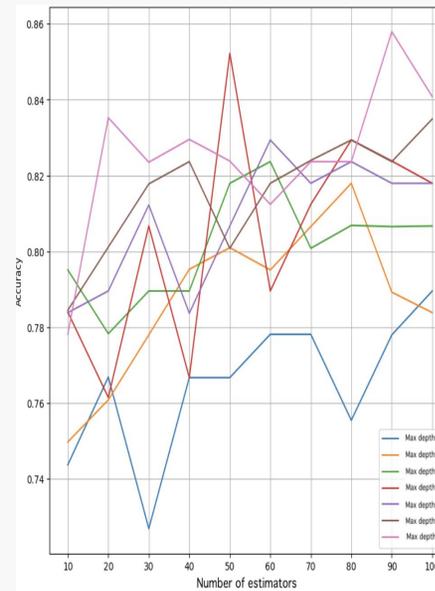
Random Forest: 85.8% accuracy

The Random Forest model's performance varies with hyperparameter tuning, and the results show that a maximum depth of 7 with 90 estimators produces the highest accuracy of 85.8%.
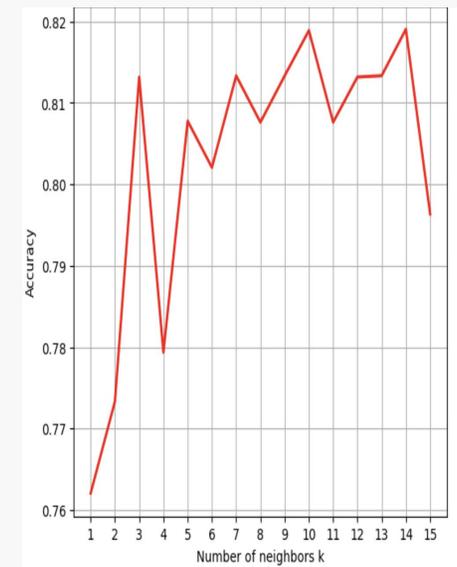
KNN: 82% Accuracy

KNN accuracy changes with the number of neighbors, and the model performs best at k = 14, where it achieves a stable accuracy of 82%.

Model Testing Results

Confusion matrices for the models, along with accuracy, precision, recall, and F1-score to assess classification performance. False negatives, mispredicting Resistant samples as susceptible, are shown in red.
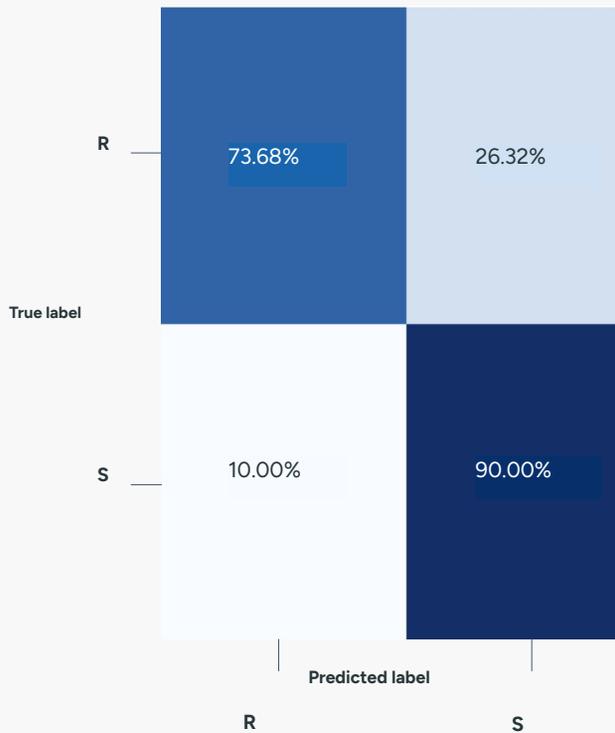
Logistic Regression: 86% Accuracy

Highest testing accuracy with strong balance across all metrics.

Precision: **0.81**

Recall: **0.82**

F1-Score: **0.81**

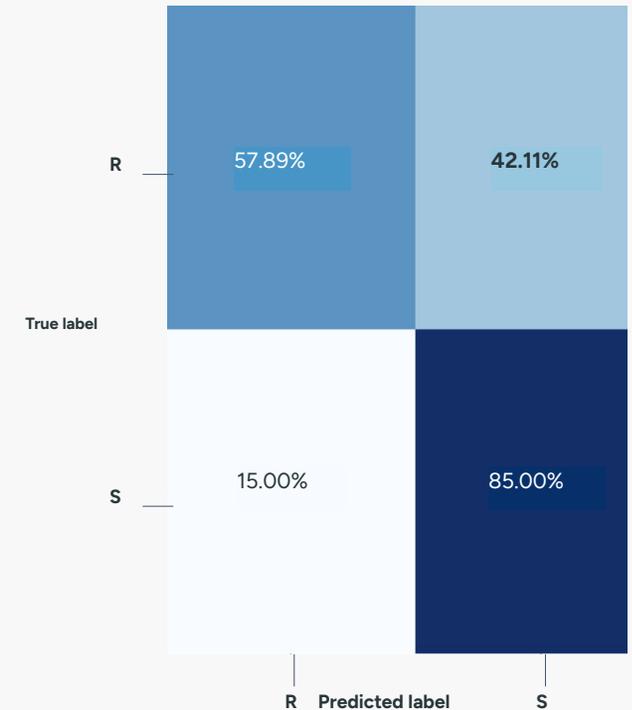False Negatives: **26.32%**

MLP: 84% Accuracy

Solid performance with nonlinear feature learning.

Precision: **0.77**

Recall: **0.80**

F1-Score: **0.79**

False Negatives: **26.32%**

Random Forest: 78% Accuracy

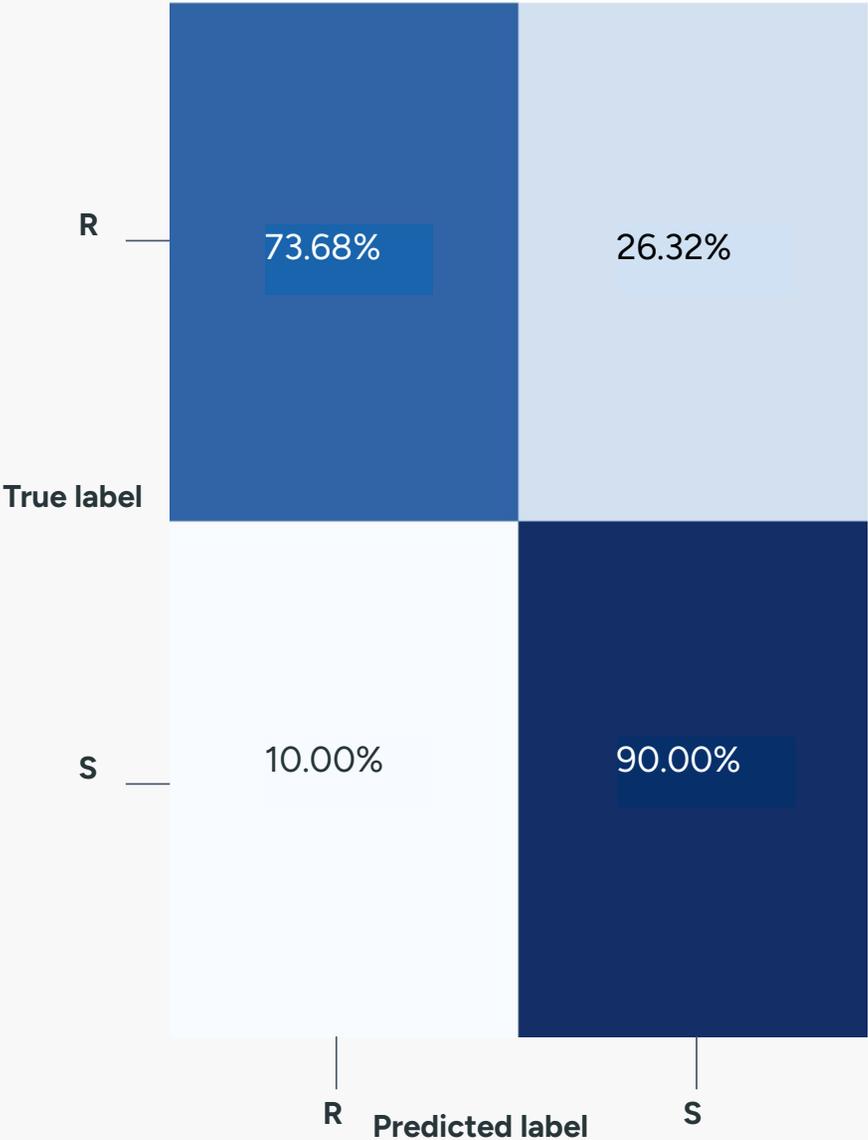Moderate accuracy with higher false negative rate.

Precision: **0.71**

Recall: **0.71**

F1-Score: **0.71**

False Negatives: **42.11%**

Why Logistic Regression Was Preferred

	R	S
R	73.68%	26.32%
S	10.00%	90.00%

True label / Predicted label

Superior Accuracy and Balance

Achieved **86% testing accuracy** with the most consistent performance across precision, recall, and F1-score metrics, outperforming both MLP and Random Forest.

Clinical Reliability

Maintained the lowest false negative rate at 26.32%, critical for clinical applications where missing resistant isolates poses serious patient safety risks.

Practical Deployment

Lightweight computational requirements enable real-time predictions on standard laboratory computers, making integration into existing clinical workflows feasible and cost-effective.

Clinical Impact and Future Directions

Immediate Clinical Value

This diagnostic utility can be integrated into existing MALDI-TOF MS methods, providing **early resistance insights** while clinicians await culture-based confirmation.

Ertapenem resistance often signals emerging broader carbapenem resistance, enabling **proactive treatment** adjustments and infection control measures.

Research Directions

Dataset Expansion: Expand data to include samples from additional hospitals covering multiple geographic regions to improve generalizability

Multi-Antibiotic Models: Extend methodology to predict resistance patterns across carbapenem family

Prospective Studies: Validate performance in real-world clinical settings with diverse patient populations

Conclusions and Significance

This research demonstrates that ertapenem resistance in Klebsiella pneumoniae can be accurately predicted from MALDI-TOF MS spectra using lightweight machine learning methods.

Proven Performance

Logistic Regression achieved 86% accuracy, providing reliable resistance detection with minimal computational overhead suitable for routine laboratory deployment.

Clinical Relevance

Focus on ertapenem addresses a critical early warning marker for carbapenem resistance, supporting faster treatment decisions and improved patient outcomes.

Scalable Solution

Integration with existing MALDI-TOF MS infrastructure requires no additional hardware, making widespread adoption feasible across diverse healthcare settings.

With further validation across diverse clinical sites and patient populations, this approach has strong potential to improve clinical decision-making and help combat the growing threat of drug-resistant infections.

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Thank You

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