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Development of a predictive model for fic index of meropenem-colistin combination against carbapenem-resistant *Acinetobacter baumannii*

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ABSTRACT

Background: Acinetobacter baumannii represents a critical antimicrobial resistance challenge in Vietnamese healthcare settings, with carbapenem resistance rates reaching 55-90%. Traditional checkerboard methodology for evaluating antibiotic combinations requires substantial time and resources, limiting routine application in research settings. Objective: To develop a predictive model for the FIC index of meropenem-colistin combination based on MIC values. Methods: A cross-sectional analytical study on 61 carbapenem-resistant A. baumannii strains (6/2022 - 12/2022). MICs were determined by broth microdilution, and synergy was evaluated through FIC index. Eight regression models were compared using 80/20 train-test split with 5-fold cross-validation for stability assessment. Results: All strains were resistant to meropenem but intermediate to colistin. The combination showed synergy in 77% and additivity in 23%. A logarithmic model FIC = 0.649 - 0.155 × ln(Mero) - 0.227 × ln(Col) achieved high accuracy (R^2 = 0.554). The model demonstrated 95% sensitivity and 75% specificity for synergy prediction with an overall classification accuracy of 88.5%. Conclusion: This is the first study applying machine learning for quantitative FIC prediction. While offering potential research applications, clinical implementation requires extensive validation, given recent evidence against therapeutic efficacy of this combination.

Keywords: *Acinetobacter baumannii, meropenem-colistin, FIC index, predictive model*

1. INTRODUCTION

Acinetobacter baumannii (*A. baumannii*) is one of the most important pathogens causing hospital-acquired infections, with high antimicrobial resistance and mortality rates that can exceed 50%. In Southeast Asia, the rates of multidrug-resistant *A. baumannii* (MDR-AB) and carbapenem-resistant *A. baumannii* (CRAB) are particularly high, at 58.51% and 64.91%, respectively [1]. In Vietnam, the carbapenem resistance situation of *A. baumannii* is alarming, with rates ranging from 55% to 90% [2].

Previously, the combination of colistin with meropenem was promising based on in vitro synergy results. The rationale for this combination was colistin's ability to disrupt bacterial cell membranes, facilitating better penetration of meropenem [3]. However, recent clinical trials such as AIDA (2018) and OVERCOME (2023) have shown that this combination offers no clinical benefit compared to colistin monotherapy [4, 5]. The latest Bayesian meta-analysis also confirms that adding meropenem does not significantly improve mortality rates [6]. Despite these clinical limitations, studying the correlation between minimum inhibitory concentration (MIC) and the FIC index of the meropenem-colistin combination retains scientific significance for several reasons: (1) understanding antimicrobial interaction mechanisms through mathematical modeling, (2) developing metho-dological frameworks for evaluating new combinations, (3) advancing quantitative approaches to drug interaction research, and (4) supporting antimicrobial stewardship programs through rational combination assessment.

Although no longer recommended for treatment, studying the correlation between minimum

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inhibitory concentration (MIC) and the FIC index of the meropenem-colistin combination remains scientifically significant. The checkerboard method, currently used to determine the FIC index, is a complex technique, requiring considerable time and resources, making it difficult to apply routinely in clinical microbiology laboratories. Previous studies have typically focused on qualitative analysis of synergy based on FIC thresholds [7, 8] while the ability to quantitatively predict FIC values from MIC has not been thoroughly investigated. Traditional checkerboard methodology requires substantial laboratory time (20 - 24 hours, including incubation, with 3 - 4 hours active laboratory work) and material costs (> 7USD per test, including reagents and labor), limiting routine application and large-scale research studies.

Various machine learning methods could be applied to predict FIC, such as linear regression, random forest, gradient boosting, or neural networks. This study chose polynomial regression for three main reasons: (1) The relationship between MIC and FIC is essentially a pharmacological interaction, often following simple mathematical principles such as linear, logarithmic, or polynomial functions; (2) With small sample sizes, complex models easily lead to overfitting and reduced stability; (3) Polynomial regression allows for easier interpretation of results through coefficients, providing better understanding of the interaction mechanisms between the two antibiotics.

This study aims to develop a polynomial regression model to predict the FIC of the meropenem-colistin combination based on the MIC values of each antibiotic. Building this predictive model can provide a more efficient and cost-effective method for evaluating antibiotic interactions while establishing a methodological foundation for studying interactions of new antibiotic combinations, though clinical application requires extensive validation, given recent evidence against therapeutic efficacy.

2. SUBJECTS AND METHODS

2.1. Study subjects

Selection criteria: The study collected *A. baumannii* strains isolated from clinical specimens, including blood, urine, sputum, wound fluid, cerebrospinal fluid, and bronchoalveolar lavage fluid from patients treated at the University Medical Center Ho Chi Minh City. The strains were isolated according to standard procedures on blood agar and MacConkey media, identified using the BD Phoenix™ system, and tested for antimicrobial resistance according to CLSI 2023 standards. Only carbapenem-resistant strains with meropenem MIC ≥ 8 µg/mL were selected. All 61 isolates from 53 patients were included in the study. For patients with multiple isolates (n = 8), each isolate represented either: (1) different anatomical sites of infection, (2) different time points during treatment, or (3) phenotypically distinct resistance patterns. This approach ensures comprehensive representation of *A. baumannii* diversity while maintaining clinical relevance. The strains were stored in the bacterial bank of the Microbiology Department at -70°C in appropriate preservation media.

Sample size and sampling method: The study collected 61 *A. baumannii* strains from 53 patients using convenience sampling. The sample size was calculated based on the formula for estimating a proportion in a population: $n \geq Z^2(1-\alpha/2)(1-p)p/d^2$, where n is the minimum sample size required; $Z(1-\alpha/2) = 1.96$ with 95% confidence; $p = 0.98$ is the synergy rate of colistin-meropenem according to Jiang et al.'s 2018 study; $d = 0.05$ is the allowable error. From this, the minimum sample size required was calculated to be 31 strains. As the number of carbapenem-resistant *A. baumannii* strains isolated during the study period exceeded the minimum sample size, all qualifying strains were collected.

Time and location of the study: The study collected clinical specimens from the Microbiology Department of the University of Medicine and Pharmacy Hospital from June to December 2022, and MIC and FIC testing was conducted from January to June 2023. The Ethics Committee for Biomedical Research at the University of Medicine and Pharmacy at Ho Chi Minh City fully endorsed our research protocol (approval number: 1005/HDDĐ-ĐHYD, dated December 9, 2022). We ensured all research activities adhered to the ethical guidelines established in the Helsinki Declaration of 1964 and its subsequent revisions.

2.2. Research methods

Study design: A cross-sectional analytical study

evaluating the in vitro synergistic effect of the meropenem-colistin combination on carbapenem-resistant *A. baumannii* strains by determining the MIC of each antibiotic and the FIC index of the antibiotic combination.

Method for determining MIC and FIC: Performed using the broth microdilution method in cation-adjusted Mueller-Hinton broth (CAMHB) on 96-well plates according to CLSI 2023 guidelines. The stock antibiotic solutions were prepared from pure materials: meropenem trihydrate ≥ 98% (Sigma-Aldrich), colistin sulfate > 19,000 units/mg (Duchefa). The dilution ranges were 0.5 - 512 µg/mL for meropenem and 0.125 - 8 µg/mL for colistin.

Determination procedure: MIC was defined as the lowest concentration of antibiotic that completely inhibited bacterial growth visible to the naked eye. Meropenem MIC was performed with final concentrations ranging from 0.25 - 256 µg/mL. Colistin MIC was performed with final concentrations ranging from 0.0625 - 4 µg/mL. FIC index was calculated using the formula: FIC = MIC of antibiotic A in combination/MIC of antibiotic A alone + MIC of antibiotic B in combination/MIC of antibiotic B alone.

Quality Control: MIC determinations were performed in single determinations due to resource constraints during the study period. This represents a methodological limitation that may affect result precision. However, quality assurance was rigorously maintained through strict adherence to CLSI 2023 guidelines, inclusion of reference strains (*E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) in each testing batch, with all results consistently falling within CLSI-acceptable ranges, and systematic validation of all laboratory procedures. Each 96-well plate included appropriate positive and negative controls, and all testing was performed by trained personnel using standardized protocols.

Classification of synergy effect based on FIC index: FIC ≤ 0.5: Synergy 0.5 < FIC ≤ 1: Additivity 1 < FIC ≤ 2: No interaction FIC > 2: Antagonism.

2.3. Data analysis methods

2.3.1. Descriptive statistics

Analysis of the distribution characteristics of meropenem and colistin MICs, distribution characteristics of the FIC of the meropenem-colistin combination, and testing for normal distribution of variables.

2.3.2. Predictive model analysis

Data was randomly divided into a training set (80%, n = 48) and a test set (20%, n = 13) to enable unbiased model evaluation. Input variables, including MIC of meropenem and colistin, were transformed into various forms: original values, square root, natural logarithm, square, cube, fourth power, and interactions between variables. Variables were normalized to the same scale before being entered into the model.

The study compared 8 multivariate linear regression models with different variable combinations. The simple linear model used only the original MIC variables of meropenem and colistin. The square root and logarithmic models used the corresponding transformed variables to capture non-linear relationships. Higher-order models added components of power 2, 3, and 4 to simulate more complex interactions. Two mixed models combined various transformations to leverage the advantages of each method.

2.3.3. Model performance evaluation

The performance of the models was comprehensively evaluated through multiple indices. The coefficient of determination R^2 assessed the ability to explain the variance of the dependent variable, with values from 0 to 1, with higher being better. Root Mean Square Error (RMSE) measures the accuracy of predictions, with units the same as the dependent variable, lower being better. These indices were calculated on all three data sets: training, testing, and combined. To evaluate model stability, 5-fold cross-validation was performed on the training set only to avoid data leakage, calculating the average R^2 and standard deviation across folds. Model selection considered test set performance, cross-validation stability, interpretability, and parsimony principles following Occam's razor.

Statistical analysis was performed using Python version 3.8 with a scikit-learn library for machine learning implementations, pandas for data manipulation, and matplotlib for visualization.

2.4. Data Management and Reproducibility

Anonymized data for all 61 *A. baumannii* isolates, including meropenem MIC, colistin MIC, actual FIC

Colistin Meropenem values, and predicted FIC values from all 8 evaluated models, will be provided upon manuscript acceptance to ensure full transparency and reproducibility.

Python scripts for data preprocessing, model training, cross-validation procedures, and performance evaluation will be made available through appropriate academic repositories with comprehensive documentation.

Detailed standard operating procedures for MIC determination, checkerboard methodology, quality control procedures, and all experimental protocols will be provided as supplementary documentation.

The datasets generated and analyzed during this study will be made available from the corresponding author upon reasonable request and manuscript acceptance, subject to appropriate ethical and institutional approvals. All analysis code and protocols will be provided to ensure full reproducibility of results.

3. RESULTS AND DISCUSSION

3.1. Characteristics of the study sample

The study collected 61 *A. baumannii* strains from 53 patients. The patient characteristics were as follows:

Table 1. Characteristics of the study sample

Characteristics	Frequency	Percentage (%)
Age (n = 53) Mean ± SD	72.3 ± 14.8	
Gender (n = 53): Male	36	67.9
Department/Unit (n = 53)		
Intensive Care Unit	29	54.7
Internal Medicine	15	28.3
Surgery	9	17.0
Diagnosis (n = 53)		
Pneumonia	36	67.9
Septicemia	19	35.8
Wound infection	10	18.9
Others	16	29.6
Specimen type (n = 61)		
Sputum	49	80.0
Blood	7	12.0
Urine	2	3.0
Others	3	5.0

The characteristics of the study sample showed a high mean age (72.3 years), predominantly male (67.9%), consistent with the study by Hafiz et al. in 2023 (mean age 69.8 years, predominantly male) [9]. *A. baumannii* was commonly isolated from respiratory specimens (80% sputum samples), associated with a high rate of pneumonia patients (67.9%) and treatment in the Intensive Care Unit (54.7%). These results are similar to the study by Koegelenberg in South Africa (respiratory isolation rate 41 - 73%) [10].

The high proportion of patients treated in the Intensive Care Unit and with pneumonia can be explained by the biological characteristics of *A. baumannii*. This bacterium prefers moist environments and has the ability to form biofilms on medical devices such as endotracheal tubes and ventilators [10]. Additionally, elderly male patients often have multiple comorbidities and immunosuppression, increasing the risk of severe infections requiring intensive care**.** These demographic characteristics are consistent with typical *A. baumannii* infections in tertiary care settings, though the single-center design may limit generalizability to other populations**.**

3.2. Characteristics of antimicrobial resistance and antibiotic interactions

Meropenem MIC ranged from 32 to ≥ 128 µg/mL, with 52.5% of strains at 64 µg/mL, 39.3% at ≥ 128 µg/mL, and 8.2% at 32 µg/mL. All strains were meropenem-resistant per CLSI 2023 standards (MIC ≥ 8 µg/mL). Colistin MIC ranged from 0.0625 to 0.25 µg/mL, with 62.3% of strains at 0.125 µg/mL, 21.3% at 0.0625 µg/mL, and 16.4% at 0.25 µg/mL. All strains were intermediate to colistin according to CLSI 2023 standards.

The meropenem-colistin combination showed synergy in 77% of strains (FIC ≤ 0.5) and additivity in 23% (0.5 < FIC ≤ 1), with no cases of antagonism. Mean FIC was 0.5 ± 0.2 (range: 0.2 - 0.9). Our synergy rate of 77% was lower than studies by Jiang et al. (98%) [11] and Abdul-Mutakabbir et al. (90%) [7], likely due to our focus on carbapenem-resistant strains with high meropenem MIC and stricter evaluation criteria (FIC ≤ 0.5 vs ≤ 0.75). However, recent clinical trials (AIDA 2018, OVERCOME 2023) show this combination provides no clinical benefits compared to colistin monotherapy, highlighting the gap between in vitro synergy and clinical efficacy [4, 5]. The latest Bayesian meta-analysis confirms that adding meropenem does not significantly improve mortality rates [6].

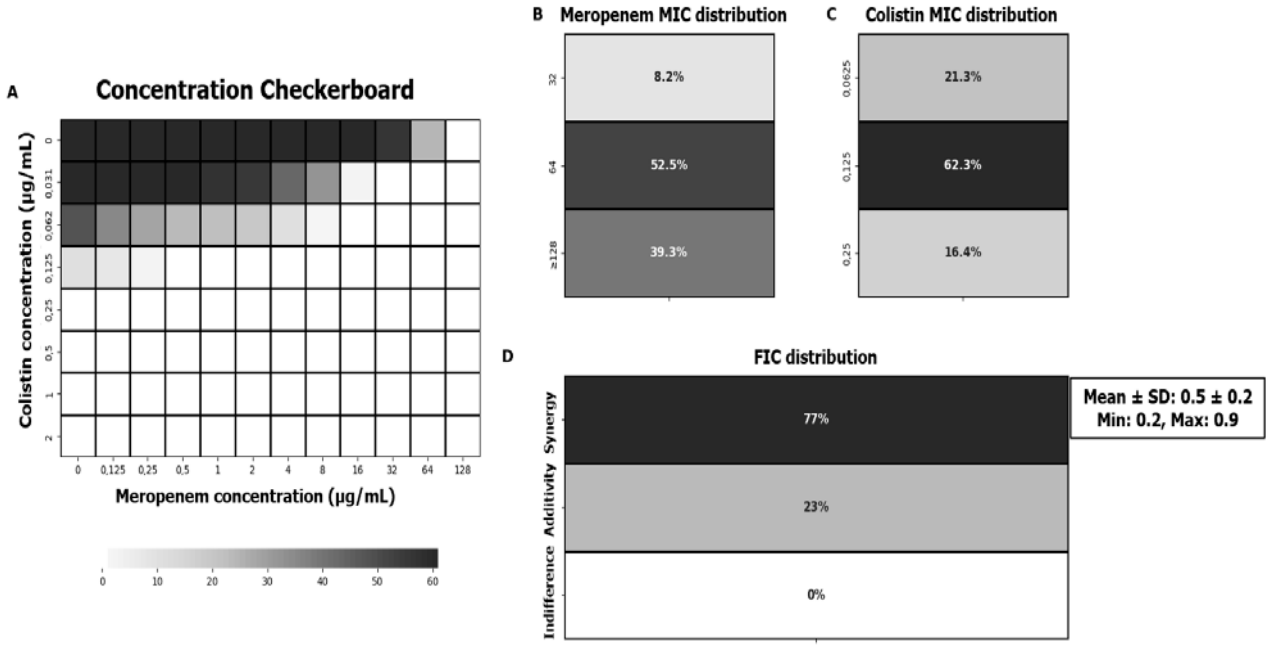

Figure 1. Analysis of interaction between colistin and meropenem on carbapenem-resistant *A. baumannii* strains

(A) Heat map showing the number of bacterial strains by colistin and meropenem concentration (darker color: More growth, lighter color: Less growth), (B) Distribution of meropenem MIC, (C) Distribution of colistin MIC, (D) Distribution of FIC of the colistin-meropenem combination, showing degrees of synergy and additivity

3.3. Results of polynomial regression analysis predicting FIC of meropenem-colistin

Table 2. Comprehensive model performance comparison

Model	R^2 Training [95% CI]	R^2 Testing [95% CI]	RMSE Testing [95% CI]	CV R^2 Mean ± SD	Classification accuracy	Sens	Spec
Logarithmic	**0.595 [0.521, 0.669]**	**0.554 [0.177, 0.931]**	**0.125 [0.089, 0.161]**	**0.441 ± 0.154**	**88.5%**	**95.0%**	**75.0%**
Fourth order	0.601 [0.524, 0.678]	0.545 [0.118, 0.972]	0.126 [0.091, 0.161]	0.409 ± 0.172	86.9%	92.5%	70.0%

Model	R^2 Training [95% CI]	R^2 Testing [95% CI]	RMSE Testing [95% CI]	CV R^2 Mean ± SD	Classification accuracy	Sens	Spec
Third order	0.601 [0.524, 0.678]	0.545 [0.118, 0.972]	0.126 [0.091, 0.161]	0.409 ± 0.172	86.9%	92.5%	70.0%
Second order	0.601 [0.524, 0.678]	0.545 [0.118, 0.972]	0.126 [0.091, 0.161]	0.409 ± 0.172	86.9%	92.5%	70.0%
Mixed 2	0.601 [0.524, 0.678]	0.545 [0.118, 0.972]	0.126 [0.091, 0.161]	0.409 ± 0.172	86.9%	92.5%	70.0%
Mixed 1	0.601 [0.524, 0.678]	0.545 [0.118, 0.972]	0.126 [0.091, 0.161]	0.409 ± 0.172	86.9%	92.5%	70.0%
Square root	0.578 [0.496, 0.660]	0.510 [0.065, 0.955]	0.131 [0.095, 0.167]	0.419 ± 0.148	83.6%	87.5%	68.8%
Linear	0.550 [0.464, 0.636]	0.453 [0.012, 0.894]	0.139 [0.102, 0.176]	0.383 ± 0.148	80.3%	82.5%	62.5%

Note: CI = Confidence Interval calculated using bootstrap resampling (n = 1000). CV = Cross-validation performed on the training set only to evaluate model stability. Classification metrics based on an FIC ≤ 0.5 threshold for synergy prediction. Bold values indicate the selected optimal model.

The study compared 8 different regression models to predict FIC from the MIC values of meropenem and colistin. The models were evaluated through performance indices on the training set, test set, and full dataset, including: Coefficient of determination (R^2), root mean square error (RMSE), mean R^2, and standard deviation of cross-validation (CV). The simple linear model had the lowest performance with R^2 = 0.453 on the test set. The logarithmic and square root models gave better results with R^2 of 0.554 and 0.510, respectively. More complex models, such as second-order, third-order, and fourth-order, yielded similar results with R^2 = 0.545.

Table 3. Mathematical formulas of models predicting FIC from MIC values

Model	Formula
Logarithmic	**FIC = 0.649 - 0.155 × ln(Mero) - 0.227 × ln(Col)**
Linear	FIC = 0.817 - 0.002 × Mero - 1.666 × Col
Square root	FIC = 1.204 - 0.033 × sqrt(Mero) - 1.277 × sqrt(Col)
Second order	FIC = 1.226 - 0.008 × Mero - 4.060 × Col + 0.000034 × $Mero^2$ + 7.520 × Col^2
Third order	FIC = 1.073 - 0.000001 × Mero - 3.899 × Col - 0.000091 × $Mero^2$ + 6.234 × Col^2 + 2.940 × Col^3
Fourth order	FIC = 1.030 - 3.882 × Col + 6.128 × Col^2 - 0.000001 × $Mero^3$ + 2.893 × Col^3 + 0.923 × Col^4
Mixed 1	FIC = 2.033 + 0.007 × Mero + 2.164 × Col - 0.154 × sqrt(Mero) - 2.906 × sqrt(Col)
Mixed 2	FIC = 1.062 + 0.002 × Mero + 0.170 × Col - 0.305 × ln(Mero) - 0.254 × ln(Col)

Note: FIC: Fractional Inhibitory Concentration; Mero: MIC of meropenem (µg/mL); Col: MIC of colistin (µg/mL); sqrt(): Square root; ln(): Natural logarithm. The coefficients in the formulas were determined by regression on the training dataset.

The logarithmic model was selected as the most appropriate due to: (1) Superior performance on the independent test set (R^2 = 0.554), (2) Reasonable cross-validation stability (CV R^2 =

0.441 ± 0.154), (3) Biological interpretability with only 2 variables, and (4) Adherence to parsimony principles compared to complex polynomial models that showed potential overfitting. Simple formula and easy to interpret:

FIC = 0.649 - 0.155 × ln(Mero) - 0.227 × ln(Col). The achieved R^2 value of 0.554 demonstrates acceptable predictive capability within the context of antimicrobial resistance research. Machine learning approaches in antimicrobial resistance prediction commonly report varying levels of performance: Nguyen et al. achieved 92% overall accuracy (within ±1 two-fold dilution factor) for MIC prediction in *Klebsiella pneumoniae* [12], while Nguyen et al. reported 95% average accuracy for MIC prediction in *nontyphoidal Salmonella* [13]. In biofilm inhibition prediction, Kumar et al. achieved a Pearson's correlation coefficient of 0.75 for IC50 prediction, equivalent to $R^2 \approx 0.56$ [14], demonstrating that our result falls within the established performance range for microbiology prediction models. The inherent biological variability in MIC determinations presents significant challenges for predictive modeling, as MIC measurements involve complexities such as 2-fold serial dilutions and measurement uncer-tainties that can limit theoretical maximum achievable accuracy, with EUCAST guidelines noting that broth MIC tests are generally re-producible to within one doubling dilution of the real end point [15]. Studies involving complex biological interactions typically report R^2 values in the 0.45 - 0.65 range due to inherent biological variability, confirming that our $R^2 = 0.554$ represents good predictive performance for this type of biological system. The cross-validation stability (CV R^2 = 0.441 ± 0.154) further supports the model's reliability, indicating consistent performance across different data subsets despite the inherent variability in microbiological assays. This level of predictive accuracy is particularly meaningful given that we are modeling complex synergistic interactions between two antibiotics, which involve multiple biological mechanisms that are not fully understood at the molecular level

This formula shows that colistin has a stronger influence on the FIC value compared to meropenem, demonstrated through the larger logarithmic coefficient (-0.227 versus -0.155). This logarithmic relationship is consistent with the biological nature of antibiotic interactions, where the effect changes according to the exponential of the concentration.

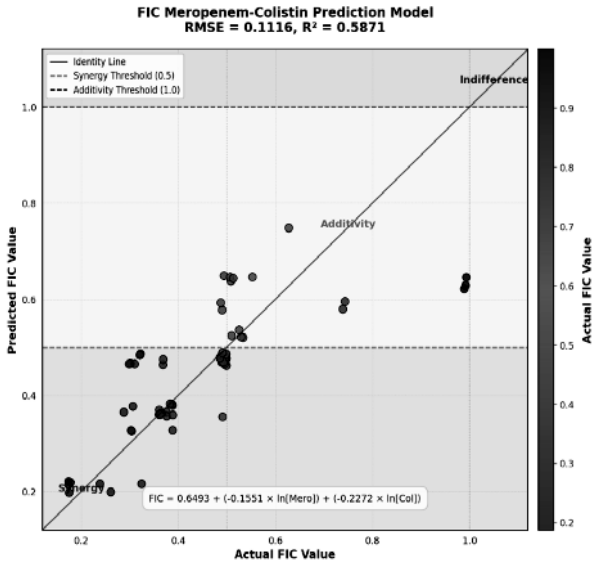

Figure 2. Model validation analysis

Scatter plot of predicted versus actual FIC values with confidence prediction bands, reference diagonal line, and clear demarcation of synergy zones (≤ 0.5), additivity zones (0.5 - 1.0), and theoretical no-interaction zones (> 1.0)

The scatter plot shows a good correlation between predicted and actual FIC values, with points distributed close to the reference line and within the synergy (FIC ≤ 0.5) and additivity (0.5 < FIC ≤ 1) zones. Low RMSE (0.125) and fairly good R^2 (0.554) on the test dataset indicate high accuracy of the model in predicting FIC values.

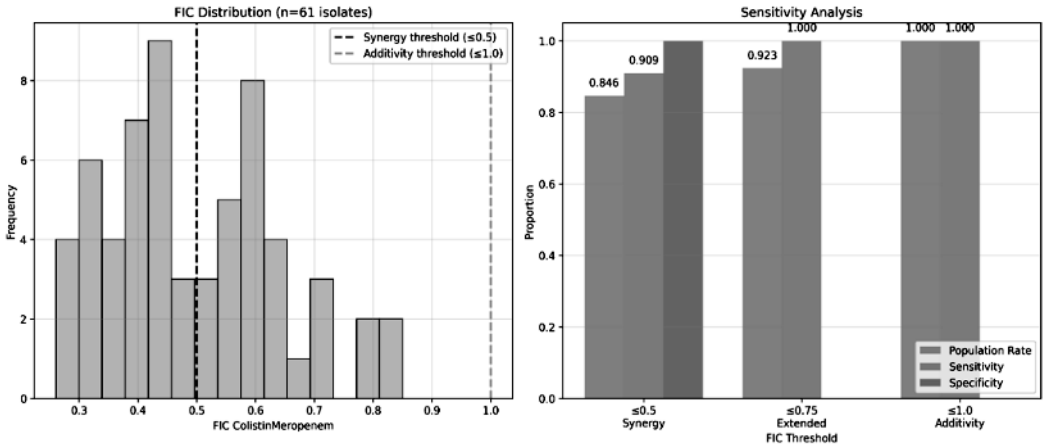

Figure 3. Sensitivity Analysis Across FIC Thresholds

Performance metrics including sensitivity, specificity, and accuracy at different synergy cutpoints (≤ 0.5, ≤ 0.75, ≤ 1.0) with corresponding population rates and clinical interpretation guidelines

Thus, in this study, the logarithmic model with the formula: FIC = 0.649 - 0.155 × ln(Mero) - 0.227 × ln(Col) was selected as the most appropriate for predicting the FIC of the meropenem-colistin combination, showing superior performance compared to 7 other models with $R^2 = 0.554$ on the test set and stability across cross-validation (CV $R^2 = 0.441 \pm 0.154$). This model simplifies the process of determining antibiotic synergy for research purposes, requiring only the MIC values of the two antibiotics as input instead of performing the entire complex checkerboard experiment, potentially reducing laboratory time by approximately 99.6% (from > 20 hours to ~5 minutes) and costs by ~98% (from >$7 to ~$0.08 per determination). For example, for a multidrug-resistant *A. baumannii* isolate with meropenem MIC = 64 µg/mL and colistin MIC = 0.125 µg/mL, the predicted FIC using our model would be: FIC = 0.649 - 0.155 × ln(64) - 0.227 × ln(0.125) = 0.476, indicating likely synergy (FIC ≤ 0.5). This allows laboratories to quickly assess potential synergy without the time-consuming checkerboard method.

The logarithmic form of the model not only provides good prediction results but also reflects the biological nature of antibiotic interactions. The higher logarithmic coefficient of colistin (-0.227) compared to meropenem (-0.155) is consistent with the key role of colistin in the synergy mechanism, disrupting bacterial cell membranes to facilitate better penetration of meropenem. The logarithmic relationship also suggests that the synergistic effect does not increase linearly with antibiotic concentration but reaches a saturation state, reflecting the limited number of binding sites on bacterial cells.

Methodologically, previous studies typically focused on qualitative analysis based on FIC thresholds to classify synergy/additivity/antagonism. Our study is one of the first to apply regression modeling methods to quantitatively predict FIC values, opening a new approach in antibiotic interaction research that provides continuous quantitative estimates rather than categorical classifications.

However, the gap between in vitro results and clinical efficacy of the meropenem-colistin combination has been demonstrated through the meta-analysis by Huang et al. (2022) [8]. This study analyzed 10 trials showing that although the meropenem-colistin combination improved microbiological response, it did not reduce mortality compared to colistin monotherapy. This may be due to several factors, such as in vivo pharmacokinetics/pharmacodynamics differing from experimental conditions, the role of the host immune system, resistance development during treatment, and complex clinical factors that cannot be captured by in vitro synergy models.

Our study has several limitations, including single-center design, small sample size (n=61, test set n=13), convenience sampling, phenotype-only analysis, and post-hoc model selection approach. These limitations indicate this model should be considered a research tool requiring extensive external validation before practical application. Future research should focus on multi-center validation with larger populations, integration of genotypic markers, extension to clinically relevant combinations, and correlation with cli-

nical outcomes.

4. CONCLUSION AND RECOMMENDATIONS

The study found that all 61 *A. baumannii* strains were meropenem-resistant but colistin-intermediate, with 77% showing synergy and 23% additivity. We developed the first quantitative FIC prediction model (FIC = 0.649 - 0.155 × ln(Mero) - 0.227 × ln(Col)) with acceptable accuracy (R^2 = 0.554, 88.5% classification accuracy) and significant efficiency gains (99.6% time reduction, 98% cost reduction) over traditional checkerboard methods. While recent clinical trials demonstrate no mortality benefit for this combination despite in vitro synergy, the modeling methodology provides valuable research tools for antimicrobial interaction studies. The model should be considered strictly for research purposes given study limitations and requires extensive validation before any practical application. This combination is not recommended for clinical use based on recent randomized controlled trials, but the predictive modeling approach establishes a foundation for future antimicrobial combination research where clinical evidence supports therapeutic benefit.

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Xây dựng mô hình dự đoán chỉ số fic của phối hợp meropenem-colistin trên *Acinetobacter baumannii* kháng carbapenem

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TÓM TẮT

Đặt vấn đề: Acinetobacter baumannii là thách thức quan trọng về kháng kháng sinh trong hệ thống y tế Việt Nam với tỷ lệ kháng carbapenem lên đến 55 - 90%. Phương pháp checkerboard truyền thống để đánh giá phối hợp kháng sinh đòi hỏi nhiều thời gian và tài nguyên, hạn chế việc ứng dụng thường quy trong các nghiên cứu. Mục tiêu nghiên cứu: Xây dựng mô hình dự đoán chỉ số FIC của phối hợp meropenem-colistin dựa trên giá trị MIC. Đối tượng và phương pháp nghiên cứu: Nghiên cứu cắt ngang phân tích trên 61 chủng Acinetobacter baumannii kháng carbapenem (6/2022 - 12/2022). Xác định MIC bằng phương pháp vi pha loãng và đánh giá hiệu quả hiệp đồng qua chỉ số FIC. Tám mô hình hồi quy được so sánh sử dụng phân chia train-test 80/20 với xác thực chéo 5-fold để đánh giá độ ổn định. Kết quả và phát hiện chính: 100% chủng kháng meropenem, trung gian với colistin. Phối hợp thể hiện hiệp đồng trên 77% và cộng hợp trên 23% số chủng. Mô hình logarit FIC = 0.649 - 0.155 × ln(Mero) - 0.227 × ln(Col) cho độ chính xác cao (R^2 = 0.554). Mô hình thể hiện độ nhạy 95% và độ đặc hiệu 75% cho dự đoán hiệp lực với độ chính xác phân loại tổng thể là 88.5%. Kết luận và kiến nghị: Đây là nghiên cứu đầu tiên áp dụng học máy dự đoán định lượng FIC. Mặc dù mang lại các ứng dụng nghiên cứu tiềm năng, việc triển khai lâm sàng đòi hỏi xác thực rộng rãi do bằng chứng gần đây chống lại hiệu quả điều trị của sự phối hợp này.

Từ khóa: *Acinetobacter baumannii, meropenem-colistin, chỉ số FIC, mô hình dự đoán*

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