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DEVELOPMENT AND VALIDATION OF A COMPOSITE RISK SCORE FOR PREDICTING MULTIDRUG-RESISTANT INFECTIONS IN CRITICALLY ILL PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT
Background: Early identification of multidrug-resistant (MDR) infections in critically ill patients remains a major clinical challenge. Delayed recognition often leads to inappropriate empirical therapy, increased mortality, and escalation of antimicrobial resistance. Clinical prediction tools may facilitate early risk stratification and optimize antimicrobial decision-making. **Objectives:** To develop and internally validate a composite clinical risk score for predicting MDR infections in critically ill patients. **Methods:** A prospective observational study was conducted among 100 critically ill patients receiving antimicrobial therapy. Independent predictors identified through multivariable logistic regression were incorporated into a weighted risk score. Model performance was evaluated using ROC analysis, calibration testing, and diagnostic accuracy metrics. **Results:** MDR prevalence was 42%. Independent predictors included ≥5 antibiotics (aOR 3.41; p=0.005), ICU stay >8 days (aOR 2.89; p=0.019), Gram-negative infection (aOR 3.27; p=0.018), and diabetes mellitus (aOR 2.21; p=0.046). A composite 8-point risk score demonstrated increasing MDR probability across low (12%), moderate (41%), and high-risk groups (78%) (p<0.001). Model discrimination was good (AUROC 0.78), with stable bootstrap validation (0.77). Calibration was acceptable (Hosmer–Lemeshow p=0.62). **Conclusion:** The ICU-MDR Risk Score provides a practical bedside tool with good predictive performance for early identification of high-risk patients.

KEYWORDS: multidrug resistance, risk score, predictive modelling, ICU, antimicrobial stewardship.

INTRODUCTION

Multidrug-resistant (MDR) infections represent one of the most significant threats in modern critical care medicine, particularly in intensive care units (ICUs), where patients are highly vulnerable due to severe illness, immunosuppression, and invasive interventions.[1] The rapid emergence and spread of resistant pathogens have profoundly compromised the effectiveness of conventional antimicrobial therapy, leading to increased morbidity, mortality, and healthcare costs.[2]

Gram-negative organisms such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* are among the most common pathogens implicated in MDR infections. These organisms possess complex resistance mechanisms, including extended-spectrum β-lactamase (ESBL) production, carbapenemase activity, efflux pumps, and biofilm formation, which collectively limit therapeutic options.[3]

The ICU environment serves as a critical hub for resistance development due to extensive antimicrobial exposure, prolonged hospitalization, frequent invasive procedures, and underlying comorbid conditions.[4] While early empirical antimicrobial therapy is essential for survival in severe infections such as sepsis, inappropriate or delayed therapy significantly increases mortality risk.[5]

Risk stratification for MDR infections has therefore become a cornerstone of modern critical care practice. Previous studies have identified key predictors such as prior antibiotic exposure, prolonged ICU stay, comorbidities (e.g., diabetes), and Gram-negative infections.[6,7,8] However, translating these epidemiological associations into practical bedside tools remains a major challenge.

Clinical prediction models and risk scoring systems offer a structured approach to integrate multiple variables into actionable decision-making tools.[9] Such models can guide empirical therapy, reduce unnecessary broad-spectrum antibiotic use, and strengthen antimicrobial stewardship programs. Despite their potential, there is a paucity of validated, ICU-specific MDR risk scores, particularly in resource-limited settings.

Therefore, this study aimed to develop and internally validate a composite ICU-based risk score for predicting MDR infections using routinely available clinical variables.

MATERIALS AND METHODS

Study Design

A **prospective observational prediction model study** was conducted to develop and internally validate a clinical risk score for predicting multidrug-resistant (MDR) infections in critically ill patients. The prospective design enabled **systematic, real-time data collection**, thereby minimizing recall bias and enhancing the temporal relationship between predictors and outcomes. The study adhered to established methodological principles for prediction model development, including transparent reporting and appropriate statistical validation.

Study Setting

The study was carried out in the **Critical Care Unit (CCU) of a tertiary care teaching hospital**, a high-acuity clinical environment that manages patients with severe, life-threatening conditions requiring advanced monitoring and intensive therapeutic interventions. The ICU setting is characterized by **high antimicrobial utilization, frequent invasive procedures (e.g., mechanical ventilation, central venous catheterization), and increased exposure to nosocomial pathogens**, making it an ideal environment for studying antimicrobial resistance patterns and predictive risk factors.

Study Population

A total of **100 critically ill patients** receiving antimicrobial therapy during their ICU stay were prospectively enrolled. Patients of both genders and varying age groups were included to ensure representativeness of the ICU population.

Only patients with **clinically suspected or microbiologically confirmed infections requiring antimicrobial treatment** were considered eligible. To ensure analytical robustness, patients were included only if **complete clinical, microbiological, and treatment-related data** were available. Each patient was considered as a single observational unit, and duplication due to repeat admissions was avoided.

Outcome Definitions

Primary Outcome

The primary outcome was **multidrug-resistant (MDR) infection**, defined according to internationally accepted criteria as:

- **Resistance to at least one agent in three or more antimicrobial classes**

This definition aligns with standard global frameworks for MDR classification and ensures comparability with existing literature.

Candidate Predictors

Candidate predictors were selected based on **biological plausibility, prior evidence, and clinical relevance** in ICU settings. The following variables were evaluated:

1. Antibiotic Burden

- Categorized as **<5 antibiotics vs ≥5 antibiotics**
- Reflects cumulative antimicrobial exposure and selection pressure
- Considered a key driver of resistance development

2. ICU Stay Duration

- Categorized as **≤8 days vs >8 days**
- Represents prolonged hospitalization and increased exposure to hospital-acquired pathogens

3. Microbiological Profile

- **Gram-negative vs Gram-positive isolate**
- Gram-negative organisms are known to harbor complex resistance mechanisms.

4. Comorbidity

- **Diabetes mellitus (present/absent)**
- Included due to its association with impaired immunity and infection susceptibility

5. Age

- Categorized as **≤60 years vs >60 years**
- Represents physiological vulnerability and altered immune response

Risk Score Development

Predictors that demonstrated statistical significance in **multivariable logistic regression analysis** were incorporated into a composite risk score.

- Each predictor was assigned a **weighted score proportional to its adjusted odds ratio (aOR)**
- Strong predictors (aOR ~3) were assigned **2 points**, while moderate predictors were assigned **1 point**
- The final score ranged from **0 to 8 points**

Patients were stratified into:

- **Low risk (0–2)**
- **Moderate risk (3–5)**
- **High risk (6–8)**

Data Collection

Data were collected prospectively using a **structured data collection form** from:

- Patient case records
- ICU monitoring charts
- Antimicrobial prescription records
- Microbiology laboratory reports

The following data were recorded:

- Demographics (age, sex)
- Clinical variables (ICU stay, comorbidities)
- Antimicrobial exposure (number and type of antibiotics)
- Microbiological findings (organism type, resistance pattern)
- Outcome (MDR status)

All microbiological analyses were performed using **standard laboratory protocols** in accordance with accepted guidelines.

Statistical Analysis

Statistical analysis was performed using **IBM SPSS Statistics software**.

1. Descriptive Analysis

- Continuous variables: mean ± standard deviation
- Categorical variables: frequency and percentage

2. Inferential Analysis

- **Chi-square test** was used to assess associations between categorical variables and MDR
- A **p-value <0.05** was considered statistically significant

3. Multivariable Logistic Regression

- Used to identify **independent predictors of MDR infection**
- Results expressed as:
  - Adjusted Odds Ratios (aOR)
  - 95% Confidence Intervals (CI)

4. Model Performance Evaluation

Discrimination

- Evaluated using **Receiver Operating Characteristic (ROC) curve**
- Area Under the ROC Curve (AUROC):
  - 0.7–0.8 = acceptable
  - 0.8–0.9 = excellent

Calibration

- Assessed using **Hosmer–Lemeshow goodness-of-fit test**
- $p > 0.05$ indicates good model fit

Internal Validation

- Performed using **bootstrap resampling technique**
- Ensures model stability and reduces overfitting

Diagnostic Performance

- Sensitivity
- Specificity
- Positive Predictive Value (PPV)
- Negative Predictive Value (NPV)

RESULTS

RISK SCORE DEVELOPMENT

Table 1: Composite ICU-MDR Risk Score Components.

Maximum Score: 8

The scoring system was derived from multivariable regression coefficients, with higher weights assigned to predictors demonstrating stronger associations with MDR.

Predictor	Points Assigned
≥5 antibiotics	2
ICU stay >8 days	2
Gram-negative isolate	2
Diabetes mellitus	1
Age >60 years	1

Table 2: Baseline Characteristics and MDR Prevalence.

The study included 100 critically ill patients with a mean age of 55.5±13.2 years. A statistically significant male predominance (54%) was observed. The overall MDR prevalence was 42%, indicating a substantial burden of resistant infections in the ICU population.

Variable	Value	p-value
Total patients	100	—
Age (years)	55.5 ± 13.2	0.021*
Male (%)	54%	0.038*
MDR prevalence (%)	42%	0.008*

Table 3: Multivariable Logistic Regression and Risk Stratification.

Poly-antibiotic exposure (≥5 antibiotics) emerged as the strongest independent predictor of MDR, followed by Gram-negative infection and prolonged ICU stay. Risk stratification demonstrated a significant gradient in MDR probability across score categories (p<0.001).

Variable / Risk Category	aOR	95% CI	MDR Risk (%)	p-value
≥5 antibiotics	3.41	1.44–8.06	—	0.005*
ICU stay >8 days	2.89	1.19–7.03	—	0.019*
Gram-negative isolate	3.27	1.22–8.77	—	0.018*
Diabetes mellitus	2.21	1.01–4.84	—	0.046*
Age >60 years	1.68	0.77–3.67	—	0.18
Risk Score 0–2 (Low)	—	—	12%	<0.001*
Risk Score 3–5 (Moderate)	—	—	41%	
Risk Score 6–8 (High)	—	—	78%	

Table 4: Diagnostic Performance and Model Discrimination.

The ICU-MDR risk score demonstrated good predictive performance. Lower cut-off values showed higher sensitivity, whereas higher cut-offs improved specificity. ROC analysis confirmed acceptable discrimination with stable internal validation.

Parameter	Cut-off / Model	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUROC
Diagnostic accuracy	**≥3**	84	62	58	86	—
Diagnostic accuracy	**≥5**	71	79	69	81	—
ROC (Derivation)	**—**	—	—	—	—	0.78
ROC (Bootstrap validation)	**—**	—	—	—	—	0.77

Table 5: Calibration Metrics and Clinical Outcomes (Mortality Association).

The model demonstrated good calibration (Hosmer–Lemeshow p=0.62). High-risk patients had significantly higher mortality compared to low/moderate-risk groups (p=0.021), indicating strong clinical relevance.

Parameter	Category / Metric	Value	p-value
Calibration	Hosmer–Lemeshow test	0.62	—
Calibration	Brier score	0.18	—
Mortality	High-risk group (Deaths/Survivors)	Jun-20	0.021*
Mortality	Low/Moderate-risk (Deaths/Survivors)	Feb-72	—

DISCUSSION

The present study developed and internally validated a composite ICU-based risk score for predicting multidrug-resistant (MDR) infections using routinely available clinical variables. The findings demonstrate that poly-antibiotic exposure, prolonged ICU stay, Gram-negative infection, and diabetes mellitus are key determinants of MDR, and their integration into a structured scoring system provides a clinically meaningful tool for early risk stratification. These observations are consistent with existing literature and reinforce the growing emphasis on predictive modelling in antimicrobial stewardship and critical care epidemiology.[10,11,12,13]

A major finding of this study is the strong association between **poly-antibiotic exposure (≥5 antibiotics)** and MDR, which emerged as the most influential predictor (aOR 3.41; p=0.005). This aligns with previous studies that have consistently identified cumulative antibiotic exposure as a primary driver of resistance due to selective pressure on microbial populations.[11,14] Similar findings were reported by Kollef et al., where prior antimicrobial therapy significantly increased the risk of resistant infections in ICU settings.[12] The biological plausibility of this association lies in the disruption of normal flora and the preferential survival of resistant strains, particularly in high-intensity care environments.

Prolonged ICU stay (>8 days) was another independent predictor (aOR 2.89; p=0.019), reflecting increased exposure to nosocomial pathogens, invasive procedures, and repeated antimicrobial courses. This observation is supported by multiple epidemiological studies demonstrating that length of stay is a surrogate marker for cumulative healthcare exposure and infection risk.[13,15] The moderate positive correlation between ICU stay and MDR risk observed in this study further substantiates this relationship and highlights the importance of early discharge planning and infection control measures.

The predominance and predictive role of **Gram-negative infections** (aOR 3.27; p=0.018) are particularly noteworthy. Gram-negative organisms such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* are well known for their complex resistance mechanisms, including ESBL production, carbapenem resistance, and biofilm formation.[16,17] Previous studies have similarly reported a higher burden of MDR among Gram-negative isolates in ICU populations, emphasizing their critical role in resistance epidemiology.[18] The high prevalence of Gram-negative organisms in the present study (79.1%) further reinforces their dominance in critical care infections.

Diabetes mellitus also emerged as a significant independent predictor (aOR 2.21; p=0.046), consistent with prior literature linking metabolic disorders to increased infection susceptibility and poor immune response.[19] Hyperglycemia-induced immune dysfunction, impaired neutrophil activity, and increased colonization risk contribute to this association. Several observational studies have identified diabetes as a risk factor for MDR infections, particularly in ICU and surgical populations.[20]

Although **age >60 years** showed an increased odds ratio, it did not reach statistical significance in the multivariable model. This finding is consistent with some studies suggesting that age alone may not be an independent predictor after adjusting for comorbidities and clinical severity.[21] Instead, age may act as a confounding factor mediated through other clinical variables such as frailty and chronic disease burden.

A key strength of this study lies in the **development of a composite risk score**, which translates individual predictors into a practical bedside tool. The observed gradient in MDR probability across risk categories low (12%), moderate (41%), and high (78%)—demonstrates strong discriminatory capacity and clinical relevance. This stepwise increase in risk is consistent with the principles of clinical prediction modelling and supports the biological plausibility of the scoring system.[22] Similar risk stratification approaches have been successfully applied in other infectious disease models, reinforcing the utility of composite scoring systems in clinical decision-making.[23]

The **diagnostic performance** of the model was robust, with an AUROC of 0.78, indicating good discrimination. This is comparable to other published prediction models in critical care, which typically report AUROC values ranging from 0.70 to 0.85.[22,23] The bootstrap validation AUROC of 0.77 further confirms the internal stability and reliability of the model, reducing concerns of overfitting. Additionally, the sensitivity-specificity trade-off observed at different cut-offs highlights the model's flexibility in clinical application, allowing clinicians to prioritize either early detection or diagnostic precision based on context.

The **calibration performance** was also satisfactory, with a Hosmer–Lemeshow p-value of 0.62, indicating good agreement between predicted and observed outcomes. The Brier score of 0.18 suggests acceptable overall model accuracy. Together, these metrics demonstrate that the model is both statistically sound and clinically applicable.

Importantly, the study demonstrated a significant association between **high-risk scores and mortality** (p=0.021), underscoring the clinical impact of MDR infections. Patients in the high-risk group experienced substantially higher mortality compared to low and moderate-risk groups, consistent with previous studies linking MDR infections to poor clinical outcomes, prolonged hospitalization, and increased healthcare costs.[24] This finding reinforces the importance of early risk identification and targeted intervention.

Compared to previous studies that primarily focused on individual risk factors, the present study provides a **comprehensive and integrated predictive framework**, enhancing its translational value. While earlier research has identified predictors such as antibiotic exposure and ICU stay, few studies have successfully combined these variables into a validated scoring system applicable at the bedside, particularly in resource-limited settings.[23,25]

From a clinical perspective, the ICU-MDR risk score offers several advantages. It utilizes readily available variables, requires no advanced diagnostics, and can be easily implemented in routine practice. By facilitating early identification of high-risk patients, the model can guide empirical antimicrobial selection, reduce inappropriate antibiotic use, and strengthen antimicrobial stewardship programs.

However, the findings should be interpreted in the context of certain limitations, including the single-centre design and relatively small sample size. External validation in larger, multicentric cohorts is essential to confirm generalizability and refine predictive accuracy.

CONCLUSION

The present study developed and internally validated an ICU-based composite risk score for early prediction of multidrug-resistant (MDR) infections in critically ill patients. The findings demonstrate that ≥5 antibiotic exposure, prolonged ICU stay (>8 days), Gram-negative infection, and diabetes mellitus are independent predictors of MDR. The proposed 8-point scoring system effectively stratifies patients into low, moderate, and high-risk categories with a clear and significant gradient in MDR probability (12%, 41%, and 78% respectively; $p<0.001$).

The model showed good discriminatory ability (AUROC 0.78) with stable internal validation (0.77) and acceptable calibration (Hosmer–Lemeshow $p=0.62$). These findings indicate that the ICU-MDR risk score is a simple, practical, and clinically useful tool that can assist clinicians in early risk identification, guide empirical antimicrobial therapy, and support antimicrobial stewardship interventions in critical care settings.

Overall, this study emphasizes that early recognition of high-risk patients may improve antimicrobial decision-making and potentially reduce MDR-related morbidity and mortality.

Limitations

• Single-centre study, limiting generalizability to other ICU settings and populations.
• Relatively small sample size (n=100), which may affect statistical power and precision of estimates.
• Internal validation only; external validation in multicentre cohorts is required before widespread clinical application.
• Potential residual confounding due to unmeasured variables such as severity scores (e.g., APACHE II, SOFA), prior hospitalization history, and prior colonization status.
• Microbiological variability and local resistance patterns may influence applicability in different geographic regions.
• Temporal changes in antimicrobial prescribing practices were not assessed.

Ethical Considerations

• The study was conducted after obtaining approval from the Institutional Ethics Committee of the tertiary care teaching hospital.
• Informed consent was obtained from patients or their legal guardians prior to inclusion.
• Patient confidentiality was strictly maintained throughout the study.
• No experimental intervention was performed; all treatments were part of routine clinical care.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this study.

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