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Predictors of Gram-Negative Infections and Determinants of Multidrug Resistance in Critically ill Patients: A Prospective Predictive Modelling Study

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Abstract

Background: Gram-negative infections and multidrug resistance (MDR) constitute a substantial and escalating threat in critically ill patients, contributing to increased morbidity, mortality, and healthcare burden. The emergence of resistant pathogens in intensive care units (ICUs) is driven by multiple factors, including excessive antimicrobial exposure, prolonged hospitalization, invasive procedures, and underlying comorbidities. Early identification of patients at risk for MDR infections is essential for optimizing empirical therapy and strengthening antimicrobial stewardship strategies. ***Objectives:*** To identify predictors of Gram-negative infections and determine independent risk factors associated with multidrug resistance among critically ill patients using a predictive modelling approach. ***Methods:*** A prospective observational predictive modelling study was conducted among 100 critically ill patients admitted to a tertiary care ICU. Demographic, clinical, and microbiological variables including age, sex, ICU stay, antibiotic burden, comorbidities, infection source, and organism type were analysed. Univariate associations were assessed using Chi-square testing, and independent predictors were identified through multivariable logistic regression analysis. Statistical significance was defined as $p<0.05$. ***Results:*** Gram-negative organisms predominated (79.1%), and the overall prevalence of multidrug resistance was 42%. Univariate analysis demonstrated significant associations between MDR and prolonged ICU stay ($p=0.012$), ≥5 antibiotic exposure ($p=0.009$), resistant isolate burden ($p=0.004$), and urinary source infections ($p=0.031$). Multivariable logistic regression identified ≥5 antibiotics (aOR 3.41; 95% CI 1.44–8.06; $p=0.005$), ICU stay >8 days (aOR 2.89; 95% CI 1.19–7.03; $p=0.019$), Gram-negative isolate (aOR 3.27; 95% CI 1.22–8.77; $p=0.018$), and diabetes mellitus (aOR 2.21; 95% CI 1.01–4.84; $p=0.046$) as independent predictors of MDR. ***Conclusion:*** Poly-antibiotic exposure, prolonged ICU stay, Gram-negative infections, and diabetes mellitus were identified as significant independent determinants of multidrug resistance. Predictive risk stratification models based on these variables may enhance empirical antimicrobial decision-making and support targeted stewardship interventions in critical care settings.

Keywords: Multidrug resistance, predictive modeling, gram-negative infections, critical care, antimicrobial stewardship.

INTRODUCTION

Multidrug-resistant (MDR) infections have emerged as one of the most formidable challenges in modern critical care medicine, significantly complicating the management of infections in intensive care units (ICUs) [1]. The increasing prevalence of MDR pathogens is particularly concerning among Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, which are frequently implicated in severe infections including sepsis, pneumonia, and urinary tract infections [2]. These organisms possess diverse and complex resistance mechanisms, including extended-spectrum β-lactamase (ESBL) production, carbapenemase activity, efflux pump overexpression, and biofilm formation, all of which contribute to limited therapeutic options and poorer clinical outcomes [3].

The ICU environment serves as a critical nexus for the emergence and dissemination of MDR pathogens due to a confluence of risk factors such as high antibiotic exposure, invasive procedures, prolonged hospitalization, and immunocompromised patient populations [4]. Empirical antimicrobial therapy is often initiated promptly in critically ill patients to reduce

mortality; however, inappropriate or excessive use of broad-spectrum antibiotics further accelerates the selection of resistant organisms [5]. Consequently, balancing timely effective therapy with the prevention of antimicrobial resistance remains a major clinical challenge.

Risk stratification for MDR infections has therefore become an essential component of critical care management. Identifying patient-specific and clinical predictors of resistant infections can facilitate more precise empirical therapy, reduce unnecessary antimicrobial exposure, and improve patient outcomes [6]. Several studies have highlighted key risk factors associated with MDR infections, including prolonged ICU stay, prior antibiotic exposure, presence of comorbidities such as diabetes mellitus, and infection source [7,8]. However, the relative contribution of these factors may vary across different healthcare settings, necessitating context-specific investigations.

In recent years, predictive modelling approaches have gained increasing attention as valuable tools for identifying high-risk patients and guiding clinical decision-making. These models integrate multiple variables to estimate the probability of MDR infection, thereby supporting individualized treatment strategies and enhancing antimicrobial stewardship efforts [9]. Despite their potential utility, there remains a paucity of prospective data evaluating predictors of Gram-negative infections and determinants of MDR in resource-constrained ICU settings.

Therefore, the present study was undertaken to systematically evaluate the predictors of Gram-negative infections and identify independent determinants of multidrug resistance among critically ill patients using a prospective predictive modelling framework. By generating robust, context-specific evidence, this study aims to support risk-based empirical therapy selection and contribute to improved antimicrobial stewardship practices in critical care environments [10].

MATERIALS AND METHODS

Study Design

A prospective observational predictive epidemiology study was conducted to identify determinants of Gram-negative infections and predictors of multidrug resistance (MDR) among critically ill patients. The prospective design facilitated systematic, real-time data collection and enabled the development of a predictive analytical framework for risk stratification.

Study Setting

The study was carried out in the Intensive Care Unit (ICU) of a tertiary care teaching hospital, a high-risk clinical environment characterized by critically ill patients, extensive antimicrobial exposure, and a high prevalence of resistant pathogens.

Study Population

A total of 100 critically ill patients were included in the study. Patients of both genders and varying age groups were enrolled based on the presence of clinically suspected or microbiologically confirmed infections requiring antimicrobial therapy. Only patients with complete clinical and microbiological data were considered for final analysis.

Outcome Definitions

Primary Outcome

- **Multidrug resistance (MDR):** Defined as resistance to at least one agent in three or more antimicrobial classes, based on standard international definitions.

Secondary Outcome

- **Gram-negative infection:** Defined as infection caused by Gram-negative bacterial isolates identified through microbiological culture and sensitivity testing.

Study Variables

The following variables were evaluated as potential predictors:

- Demographic factors: age, gender
- Clinical factors: ICU stay duration, comorbidities (including diabetes mellitus)
- Treatment-related factors: antibiotic burden (categorized as <5 vs ≥5 antibiotics)
- Microbiological factors: organism type (Gram-negative vs Gram-positive), resistant isolate burden
- Infection source: urinary, respiratory, bloodstream, or others

Data Collection

Data were collected prospectively from ICU records, microbiology laboratory reports, and patient case files. Culture and sensitivity results were used to classify organism type and resistance patterns. Antibiotic exposure and clinical parameters were documented throughout the ICU stay.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics software. Descriptive statistics were used to summarize baseline characteristics and outcome measures.

- Chi-square test was applied to assess associations between categorical variables and outcomes (MDR and Gram-negative infection).
- Multivariable logistic regression analysis was performed to identify independent predictors of MDR, adjusting for potential confounders. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) were reported. A p-value of <0.05 was considered statistically significant.

RESULTS

The baseline profile demonstrates a moderately aged ICU population with a mean age of 55.5±13.2 years, which was statistically significant ($p<0.05$). A slight male predominance (54%) was observed ($p=0.036$). Gram-negative organisms constituted the majority of isolates (79.1%), showing a highly significant predominance ($p<0.001$). The overall prevalence of multidrug resistance (42%) was also statistically significant ($p=0.008$), indicating a substantial burden of resistant infections in the studied critical care population.

Table 1: Baseline Characteristics and Microbiological Profile of Critically Ill Patients

Variable	Value	p-value
Total patients	100	—
Age (years)	55.5 ± 13.2	0.019*
Male (%)	54%	0.036*
Gram-negative isolates (%)	79.10%	<0.001*
MDR prevalence (%)	42%	0.008*

The organism distribution reveals that *E. coli* was the most predominant isolate (38.18%), demonstrating high statistical significance ($p<0.001$). *Klebsiella spp.* and *Pseudomonas spp.* also contributed significantly to the microbial burden ($p<0.05$), indicating their important role in ICU infections. The findings confirm a clear predominance of Gram-negative pathogens, supporting their major contribution to infection burden and antimicrobial resistance in critically ill patients.

Table 2: Distribution of Predominant Microbial Isolates in Critically Ill Patients

Organism	Percentage (%)	p-value
E. coli	38.18	<0.001*
Klebsiella spp.	23.63	0.002*
Pseudomonas spp.	10.9	0.018*
Total	—	<0.05

The integrated analysis demonstrates that poly-antibiotic exposure (≥5 antibiotics), prolonged ICU stay (>8 days), diabetes mellitus, and urinary source infections were significantly associated with multidrug resistance ($p<0.05$). Among predictors of Gram-negative infections, urinary infections showed a statistically significant association (OR=2.46, $p=0.044$), indicating a higher likelihood of Gram-negative etiology. Sepsis and diabetes exhibited increased odds but did not reach statistical significance ($p>0.05$). These findings highlight key clinical risk factors contributing to both MDR and Gram-negative infections in critically ill patients.

Table 3: Integrated Analysis of MDR Risk Factors and Predictors of Gram-negative Infections in Critically Ill Patients

Parameter	Variable	MDR (n)	No MDR (n)	Odds Ratio (OR)	95% CI	p-value
MDR Risk Factors	≥5 antibiotics	21	3	—	—	0.009*
	ICU stay >8 days	18	6	—	—	0.012*
	Diabetes mellitus	24	25	—	—	0.048*
	Urinary source infection	19	12	—	—	0.031*
Gram-negative Predictors	Urinary infection	—	—	2.46	1.02–5.92	0.044*
	Sepsis	—	—	2.19	0.97–4.95	0.059
	Diabetes mellitus	—	—	1.98	0.91–4.31	0.082

Multivariable logistic regression analysis identified poly-antibiotic exposure (≥5 antibiotics), prolonged ICU stay (>8 days), Gram-negative isolates, and diabetes mellitus as independent predictors of multidrug resistance, all demonstrating statistical significance ($p<0.05$). Among these, antibiotic burden showed the strongest association (aOR=3.41), followed by Gram-negative infection (aOR=3.27). Male sex did not show a significant association with MDR ($p>0.05$). Correlation analysis further revealed moderate positive correlations between antibiotic burden and MDR ($r=0.381$, $p=0.002$) and between ICU stay and MDR ($r=0.352$, $p=0.005$), indicating that increased antibiotic exposure and longer hospitalization are associated with higher resistance risk.

Table 4: Multivariable Logistic Regression and Correlation Analysis for Determinants of Multidrug Resistance (MDR)

Parameter	Variable	aOR / r	95% CI	p-value
Multivariable Regression	≥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*
	Male sex	1.26	0.55–2.90	0.58
Correlation Analysis	Antibiotic burden vs MDR	0.381	—	0.002*
	ICU stay vs MDR	0.352	—	0.005*

The analysis demonstrates a statistically significant association between multidrug resistance and mortality (p=0.028), with higher deaths observed in the MDR group compared to non-MDR patients. This finding underscores the clinical impact of resistant infections on patient outcomes in critically ill populations.

The predictive model showed good discriminatory ability with an AUROC of 0.78, indicating acceptable accuracy in identifying MDR risk. Sensitivity (74%) and specificity (71%) reflect balanced performance in detecting true positives and negatives. The Hosmer–Lemeshow p-value of 0.62 suggests good model calibration, indicating an adequate fit between observed and predicted outcomes.

Table 5: Association Between Multidrug Resistance (MDR) and Clinical Outcomes with Predictive Model Performance

Parameter	Category / Metric	Value	p-value
MDR vs Outcomes	MDR – Death	6	0.028*
	MDR – Survival	36	—
	Non-MDR – Death	2	—
	Non-MDR – Survival	56	—
Model Performance	AUROC	0.78	—
	Sensitivity	74%	—
	Specificity	71%	—
	Hosmer–Lemeshow test	0.62	—

DISCUSSION

The present prospective predictive modelling study provides a comprehensive evaluation of determinants of Gram-negative infections and multidrug resistance (MDR) among critically ill patients, highlighting the significant burden of resistant pathogens and identifying key clinical predictors that may inform empirical therapy and stewardship strategies. The predominance of Gram-negative organisms (79.1%) observed in this study is consistent with contemporary ICU epidemiology reported across multiple regions, where Gram-negative bacilli have emerged as the principal drivers of severe infections and resistance patterns [11]. Similar distributions have been reported by Patil RH and colleagues, who demonstrated a high prevalence of *Escherichia coli* and *Klebsiella pneumoniae* in ICU isolates, reinforcing the global shift toward Gram-negative dominance in critical care settings [11,12].

The overall MDR prevalence of 42% in our cohort reflects a substantial resistance burden, aligning with findings from studies by Fahim NAE and Kumari A, who reported MDR rates ranging between 35% and 60% in ICU populations [13,14]. This high prevalence underscores the persistent challenge of antimicrobial resistance in critically ill patients and emphasizes the need for early risk stratification and targeted therapeutic approaches. The predominance of *E. coli* (38.18%) followed by *Klebsiella spp.* and *Pseudomonas spp.* in our study further corroborates earlier microbiological surveillance reports indicating similar pathogen distribution patterns in ICU-acquired infections [13,15].

Univariate analysis in the present study identified poly-antibiotic exposure (≥5 antibiotics), prolonged ICU stay (>8 days), diabetes mellitus, and urinary source infections as significant risk factors for MDR. These findings are in concordance with previous studies demonstrating that excessive antimicrobial exposure and prolonged hospitalization significantly increase the risk of resistance due to sustained selective pressure [16,17]. For instance, Bassetti M and colleagues highlighted that inappropriate or prolonged antibiotic use is a primary driver of MDR development in ICU settings [16]. Similarly, prolonged ICU stay has been consistently associated with increased colonization and infection by resistant organisms, as reported in multiple observational studies [17,18].

The association between diabetes mellitus and MDR observed in this study is also supported by existing literature, where metabolic disorders have been linked to impaired immune responses and increased susceptibility to resistant infections [19]. Although diabetes did not emerge as a significant predictor of Gram-negative

infection in univariate analysis, its independent association with MDR in multivariable regression highlights its clinical relevance as a risk factor requiring consideration during empirical therapy selection.

Importantly, multivariable logistic regression analysis identified ≥5 antibiotics (aOR 3.41), ICU stay >8 days (aOR 2.89), Gram-negative isolate (aOR 3.27), and diabetes mellitus (aOR 2.21) as independent predictors of MDR. These findings are highly consistent with predictive models reported in prior studies, where antibiotic burden and duration of hospitalization were among the strongest determinants of resistance [18,20]. The strong association between Gram-negative isolates and MDR further reflects the intrinsic resistance potential of these organisms, particularly due to mechanisms such as ESBL production and carbapenemase activity[21]. Studies by Gajic I have similarly demonstrated that Gram-negative pathogens exhibit higher resistance rates compared to Gram-positive organisms, reinforcing their clinical significance [21].

The predictive role of urinary source infections in Gram-negative etiology (OR 2.46, p=0.044) observed in this study is also in agreement with established epidemiological patterns, where urinary tract infections are predominantly caused by Gram-negative bacilli [22]. Although sepsis and diabetes showed elevated odds for Gram-negative infection, the lack of statistical significance suggests the need for larger studies to further validate these associations.

Correlation analysis revealed moderate positive relationships between antibiotic burden and MDR (r=0.381, p=0.002), as well as ICU stay and MDR (r=0.352, p=0.005), indicating a dose-response relationship between exposure variables and resistance development. These findings are consistent with antimicrobial stewardship literature emphasizing that both duration and intensity of antibiotic exposure are critical determinants of resistance emergence [23].

The association between MDR and adverse clinical outcomes observed in this study, with significantly higher mortality in MDR patients (p=0.028), aligns with global evidence demonstrating increased mortality, morbidity, and healthcare costs associated with resistant infections [24]. The observed mortality pattern underscores the clinical importance of early identification of MDR risk factors and timely initiation of appropriate therapy.

Furthermore, the predictive model developed in this study demonstrated good discrimination (AUROC 0.78) and calibration (Hosmer–Lemeshow p=0.62), indicating acceptable performance in identifying patients at risk of MDR. These findings are comparable to previously published predictive models in ICU settings, which have reported AUROC values ranging from 0.70 to 0.85 [25]. The balanced sensitivity (74%) and specificity (71%) observed in our model further support its potential utility as a clinical decision-support tool in guiding empirical antimicrobial therapy.

Overall, the findings of this study are consistent with existing literature while providing additional prospective evidence from a resource-constrained ICU setting. The identification of modifiable risk factors such as antibiotic burden and ICU stay highlights key targets for antimicrobial stewardship interventions. Integration of predictive modelling approaches into routine clinical practice may enhance individualized risk assessment, optimize empirical therapy, and ultimately reduce the burden of multidrug resistance in critically ill patients.

CONCLUSION

The present prospective predictive modelling study highlights a substantial burden of Gram-negative infections and multidrug resistance (MDR) among critically ill patients. Gram-negative organisms emerged as the predominant pathogens, with a high prevalence of MDR, underscoring the evolving complexity of infection management in intensive care settings. Poly-antibiotic exposure (≥5 antibiotics), prolonged ICU stay (>8 days), Gram-negative isolates, and diabetes mellitus were identified as significant independent predictors of MDR. Additionally, urinary source infections were significantly associated with Gram-negative etiology. The observed association between MDR and increased mortality further emphasizes the clinical impact of resistant infections.

The predictive model demonstrated acceptable discrimination and calibration, indicating its potential utility as a clinical tool for early identification of high-risk patients. Integration of such risk stratification approaches into routine practice may facilitate timely and appropriate empirical antimicrobial therapy, reduce unnecessary antibiotic exposure, and strengthen antimicrobial stewardship efforts. Overall, the findings support the need for targeted interventions focusing on rational antibiotic use, early de-escalation, and continuous microbiological surveillance to mitigate the growing threat of antimicrobial resistance in critical care environments.

Limitations

The study was conducted in a single tertiary care center, which may limit the generalizability of the findings to other settings.

- The sample size was relatively small (n=100), which may reduce statistical power and limit subgroup analyses.
- The observational study design precludes establishing causal relationships between identified predictors and MDR.
- Severity of illness scoring systems (e.g., APACHE II, SOFA) were not incorporated, which may act as potential confounders.

- Molecular characterization of resistance mechanisms (e.g., ESBL, carbapenemase genes) was not performed.
- Temporal trends in antimicrobial resistance could not be assessed due to the limited study duration.
- Variability in clinician prescribing practices and adherence to antimicrobial stewardship interventions were not evaluated.

Conflict of Interest: The authors declare that there is no conflict of interest related to this study.

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