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Original Research Article

# The Resistant Threat in Critical Care: Comprehensive Mapping of the Burden and Outcomes of Multidrug-Resistant Infections in ICU Patients

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**Abstract**

**Background:** Multidrug-resistant organism (MDRO) infections are increasingly prevalent in intensive care units (ICUs), posing significant therapeutic and prognostic challenges. Data from low- and middle-income countries remain limited despite carrying a disproportionate global burden.

**Objectives:** To estimate the prevalence of MDRO infections in ICU patients, assess their impact on mortality and clinical outcomes, and identify predictors of infection and death.

**Methods:** This prospective, observational cohort study was conducted over 18 months in a tertiary-care ICU. Adult patients (≥18 years) with culture-positive bacterial infections were enrolled (N=327). MDR status was defined according to CDC/ECDC criteria. Demographics, comorbidities, APACHE II/SOFA scores, device use, and microbiological data were collected. Outcomes included ICU mortality, length of ICU/hospital stay, ventilator days, and complications. Statistical analysis employed Chi-square and t-tests for group comparisons, Kaplan–Meier survival analysis, and multivariate logistic regression to identify predictors of MDR acquisition and mortality.

**Results:** Of 327 patients, 146 (44.6%) had MDRO infections. Gram-negative pathogens predominated: Acinetobacter baumannii (28.1%), Klebsiella pneumoniae (24.7%), and Pseudomonas aeruginosa (19.2%). Carbapenem resistance was alarmingly high in Acinetobacter (89.5%) and Klebsiella (76.3%). Compared to non-MDR infections, MDRO infections were associated with higher ICU mortality (47.9% vs. 28.2%, $p<0.001$), prolonged ICU stay (19.8 vs. 13.4 days, $p<0.001$), hospital stay (28.6 vs. 21.3 days, $p<0.001$), and ventilator days (14.7 vs. 9.2, $p<0.001$). Complications such as septic shock (39.7% vs. 21.5%), renal replacement therapy (18.5% vs. 9.9%), and secondary infections (25.3% vs. 12.7%) were significantly more common. Independent predictors of mortality among MDR patients included septic shock (OR 3.24, 95% CI 1.76–5.95), carbapenem resistance (OR 2.87, 95% CI 1.52–5.41), APACHE II >25 (OR 2.54, 95% CI 1.33–4.82), and renal replacement therapy requirement (OR 2.11, 95% CI 1.05–4.22).

**Conclusions:** Nearly half of ICU infections were caused by MDROs, doubling mortality and significantly increasing ICU burden. Septic shock and carbapenem resistance were the most ominous predictors of death. These findings underscore the urgent need for rapid diagnostics, tailored empiric therapy, strict infection-control bundles, and robust antimicrobial stewardship in critical care settings.

**Keywords:** Multidrug-resistant organisms, ICU infections, carbapenem resistance, mortality predictors, antimicrobial stewardship.

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## Introduction

Intensive care units (ICUs) are the epicenters of modern hospital care, providing life-saving support to critically ill patients. However, these settings are also highly vulnerable to hospital-acquired infections (HAIs), particularly those caused by multidrug-resistant organisms (MDROs). The emergence of MDROs—including carbapenem-resistant Klebsiella pneumoniae, Acinetobacter

baumannii, Pseudomonas aeruginosa, and methicillin-resistant Staphylococcus aureus (MRSA)—has created a global health crisis. These pathogens thrive in ICUs where broad-spectrum antibiotics are frequently used, invasive procedures are common, and patients are immunocompromised. According to WHO, antimicrobial resistance accounted for 1.27 million deaths globally in 2019, with a disproportionately high burden in LMICs where ICU infection control resources may be limited [13].

**Epidemiology and Global Burden:** The prevalence of MDRO infections in ICUs varies widely but is universally high. A multicenter study reported that up to 40% of ICU infections were caused by MDR Gram-negative pathogens [8]. In Latin American ICUs, MDRO colonization and infection rates range from 15–30%, with associated mortality as high as 38% [2,4]. Asian surveillance studies reveal similar trends, with Acinetobacter and Klebsiella dominating resistant isolates. Ventilator-associated pneumonia (VAP), central line–associated bloodstream infections (CLABSI), and catheter-associated urinary tract infections (CAUTI) are the most common ICU-acquired infections, with VAP mortality ranging between 33–50%, particularly when MDR organisms are involved [16,17]. These figures highlight that MDROs are not only frequent but also linked to worse outcomes compared to susceptible infections.

**Pathogenesis and Mechanisms of Resistance:** MDROs in ICUs often belong to the so-called ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.), so named for their ability to "escape" the effects of antimicrobial therapy [14]. Mechanisms of resistance include β-lactamase production (ESBL, carbapenemase), efflux pumps, porin mutations, and biofilm formation on indwelling devices. These mechanisms lead not only to treatment failure but also to cross-transmission between patients through healthcare workers' hands, ventilator circuits, or contaminated surfaces. The ICU environment thus becomes a perfect storm for resistance development and dissemination.

**Clinical Consequences:** The outcomes of MDRO infections in critically ill patients are devastating. Studies demonstrate significantly higher mortality rates in patients with MDRO infections compared to those infected with susceptible organisms—ranging from 30% to 70% depending on pathogen and site of infection [5,7,9]. In one cohort, MDR respiratory tract infections resulted in longer durations of mechanical ventilation (18 vs. 12 days), prolonged ICU stay (23 vs. 16 days), and markedly higher mortality (73% vs. 53%) compared to susceptible infections [5]. Similar findings have been echoed in bloodstream infections, where mortality increased from 27.9% in non-MDR cases to 38.8% in MDR cases [2]. Moreover, infections with resistant Gram-negatives such as CRKP or carbapenem-resistant Acinetobacter can push mortality beyond 40–50% [18].

The morbidity burden is equally concerning. MDRO infections extend ICU and hospital length of stay, inflate healthcare costs, and delay recovery. For example, one study estimated ICU length of stay to increase from 16 days in non-infected patients to 44 days in those with MDR bloodstream infections [7]. These prolonged stays expose patients to additional risks, create bed shortages, and strain already resource-limited ICUs, particularly in low- and middle-income countries.

**Risk Factors:** Several factors predispose ICU patients to MDRO infections. Prolonged ICU stay, mechanical ventilation, vasopressor use, prior broad-spectrum antibiotic exposure, presence of invasive lines (central venous catheters, urinary catheters), and comorbidities such as diabetes, chronic kidney disease, and immunosuppression have been repeatedly identified as predictors [3,5,10]. Interestingly, while antibiotic exposure is strongly associated with acquisition of MDR colonization, some studies suggest it may not independently predict mortality [10]. This indicates that patient severity, device use, and ICU length of stay are more important determinants of adverse outcomes.

**Therapeutic Challenges:** Treatment of MDRO infections in ICUs is often empirical and complicated by limited antibiotic options. Agents such as colistin, tigecycline, and newer β-lactam/β-lactamase inhibitor combinations may be effective, but concerns about nephrotoxicity, resistance development, and cost persist [18].

Juggling between inadequate early empiric therapy and antibiotic overuse that fosters further resistance presents an ongoing dilemma. The Infectious Diseases Society of America (IDSA) guidelines stress the importance of individualized therapy, rapid diagnostics, and antimicrobial stewardship to mitigate these challenges [18].

**Infection Control and Prevention:** Prevention is critical in combating MDR infections in ICUs. Active surveillance, strict hand hygiene, isolation precautions, and antimicrobial stewardship programs have been shown to reduce MDRO prevalence [3]. For example, universal decolonization strategies in MRSA endemic settings and ventilator care bundles for VAP prevention are effective measures. However, compliance remains variable across ICUs

worldwide. In resource-constrained hospitals, lack of infection control infrastructure and antibiotic misuse exacerbate the problem, making stewardship and preventive bundles even more urgent.

**Rationale for the Present Study:** Despite a growing body of literature, there remain important gaps. Most studies are single-center, focus on a specific pathogen, or report outcomes in limited subgroups. Few have systematically compared prevalence, risk factors, and outcomes across multiple MDROs in critically ill populations. Moreover, regional data from South Asia and India remain scarce, despite these regions carrying some of the highest global burdens of antimicrobial resistance [13].

### Objectives

This study was therefore designed to:

1. Estimate the prevalence of multidrug-resistant infections among ICU patients.
2. Assess the clinical outcomes of these infections, including mortality, length of ICU/hospital stay, and duration of mechanical ventilation.
3. Identify risk factors and predictors associated with MDRO infections and adverse outcomes.
4. Provide evidence to guide antimicrobial stewardship, infection control, and policy-making in ICU practice.

## Materials and Methods

### Study Design

- A prospective, observational, cohort study
- Study period: 18 months
- The study adhered to STROBE guidelines for observational research.

### Study Population

### Inclusion Criteria

- Adult patients (≥18 years) admitted to ICU with suspected or confirmed infection.
- Positive culture results from clinical specimens (blood, respiratory secretions, urine, wound swabs, or catheter tips).
- Availability of antimicrobial susceptibility testing.

### Exclusion Criteria

- Patients with ICU stay <48 hours.
- Culture-negative sepsis or fungal-only infections.
- Patients previously enrolled in the study during an earlier ICU admission.

### Sample Size Estimation

- Using Cochran's formula for prevalence studies with an assumed MDR infection prevalence of 30% [8], margin of error 5%, and 95% confidence level, the minimum sample size was estimated at 323 patients.
- To account for attrition and culture-negative cases, the target enrollment was set at 350 patients.

### Definitions

- **Multidrug-resistant organism (MDRO):** Non-susceptibility to at least one agent in three or more antimicrobial categories, as per CDC/ECDC criteria.
- **ICU-acquired infection:** Infection developing ≥48 hours after ICU admission.
- **Clinical outcomes:** ICU mortality, length of ICU stay, duration of mechanical ventilation, and hospital length of stay.

### Data Collection

- Demographics: age, sex, comorbidities (diabetes, CKD, malignancy, immunosuppression).
- Clinical details: primary diagnosis, APACHE II and SOFA scores on admission, vasopressor requirement, and device use (endotracheal tube, central line, and urinary catheter).
- Microbiological data: site of infection, organism isolated, antimicrobial susceptibility pattern.
- Outcomes: survival status at ICU discharge, length of ICU/hospital stay, ventilator days, complications.

### Laboratory Methods

- Specimens were processed in the Microbiology Department following CLSI guidelines.
- Identification performed by automated systems (VITEK 2, bioMérieux) and conventional biochemical methods.
- Antimicrobial susceptibility tested using Kirby–Bauer disk diffusion and MIC determination (broth microdilution).
- MDR, XDR, and PDR classification per Magiorakos et al., 2012 definitions.

### Outcome Measures

**Primary Outcome**: Prevalence of MDR infections among ICU patients.

### Secondary Outcomes

- ICU mortality associated with MDR vs non-MDR infections.
- Impact on ICU length of stay and duration of mechanical ventilation.
- Identification of independent predictors of MDR infection and mortality.

### Ethical Considerations

- Approval obtained from the Institutional Ethics Committee (IEC) of Smt. Kashibai Navale Medical College.
- Written informed consent obtained from patient relatives, given critical illness of participants.
- Confidentiality maintained; data anonymized for analysis.

**Statistical Analysis**

- Data analyzed using SPSS version 26.0 (IBM, USA).
- Continuous variables expressed as mean ± SD or median (IQR), compared using Student's t-test or Mann–Whitney U test as appropriate.
- Categorical variables expressed as frequency (%), compared using Chi-square test or Fisher's exact test.
- Kaplan–Meier survival analysis used for ICU mortality.
- Multivariate logistic regression performed to identify predictors of MDR infection and mortality (variables with $p<0.1$ in univariate analysis included).
- Statistical significance defined as $p < 0.05$.

**Results**

**Study Population and Flow of Patients:** During the 18-month study period, 402 patients were admitted to the adult ICU. After applying eligibility criteria, 350 patients were recruited. Among them, 327 patients yielded culture-positive bacterial isolates and were therefore included in the final analysis, while 23 had sterile or fungal-only cultures and were excluded.

Of the 327 patients, 146 (44.6%) were infected with multidrug-resistant organisms (MDROs), while 181 (55.4%) had infections caused by non-MDRO pathogens. This indicates that nearly one out of every two critically ill patients with culture-positive infection in our ICU was infected with an MDRO, highlighting the magnitude of the resistance problem.

The mean age of patients was 52.4 ± 15.3 years (range: 18–84 years), and there was a male predominance (60.2%). The distribution of comorbidities was typical of a critical care cohort: diabetes mellitus (28.1%), chronic kidney disease (16.8%), malignancy (9.2%), and chronic obstructive pulmonary disease (8.6%). Importantly, disease severity was similar between MDR and non-MDR groups, with comparable APACHE II (22.3 vs. 21.5) and SOFA scores, confirming that differences in outcomes are attributable to infection status rather than baseline severity.

**Prevalence and Microbiological Distribution:** The prevalence of MDRO infection (44.6%) in our ICU mirrors findings from earlier Indian and international studies that report rates between 40–60% [8,9]. Gram-negative pathogens dominated, with the most frequent isolates being Acinetobacter baumannii (28.1%), Klebsiella pneumoniae (24.7%), and Pseudomonas aeruginosa (19.2%). Among Gram-positives, MRSA accounted for 10.3%.

The predominance of Gram-negative MDR pathogens is clinically significant. These organisms thrive in ICU environments where ventilators, catheters, and prolonged antibiotic exposure create selective pressures. Respiratory infections were the most common site (48.6%), followed by bloodstream (27.2%), urinary tract (14.1%), and surgical/wound infections (10.1%). This distribution emphasizes that respiratory tract remains the primary battlefield of ICU antimicrobial resistance, consistent with ventilator-associated pneumonia being the most frequent ICU-acquired infection [16].

**Antibiotic Susceptibility:** Resistance to carbapenems was alarmingly high, particularly in Acinetobacter (89.5%) and Klebsiella (76.3%). Colistin remained the most reliable agent (>90% susceptibility), but its use is limited by nephrotoxicity and concerns about emerging resistance. Aminoglycosides demonstrated moderate efficacy, whereas fluoroquinolones and cephalosporins were largely ineffective.

This antibiotic profile highlights a shrinking therapeutic arsenal, forcing intensivists to rely on last-resort drugs. Among Gram-positives, MRSA isolates were fully susceptible to vancomycin and linezolid, aligning with global trends of preserved activity of these agents against resistant staphylococci.

**Mortality Outcomes:** ICU mortality was significantly higher in the MDR group (47.9%) compared with the non-MDR group (28.2%) ($p<0.001$). The highest mortality was observed with carbapenem-resistant Acinetobacter (61.0%) and CRKP (55.6%), reflecting their notorious virulence and limited treatment options.

Survival analysis (Kaplan–Meier) showed consistently poorer outcomes for MDR-infected patients, with median survival reduced by 8 days compared to non-MDR infections. These results underscore that MDR infection is not just a microbiological label but a strong determinant of survival in the ICU.

**Impact on ICU Course**

MDR infections exerted a heavy toll on ICU resources:

- ICU stay was prolonged by nearly a week (19.8 vs. 13.4 days, $p<0.001$).

- Hospital stay extended by almost 8 days (28.6 vs. 21.3 days, p<0.001).
- Mechanical ventilation was required longer (14.7 vs. 9.2 days, p<0.001).

Each of these parameters—ventilator days, ICU stay, hospital stay—not only reflects disease severity but also increases cost of care, risk of secondary complications, and burden on ICU beds. These findings confirm the well-established association between MDRO infections and resource utilization, aligning with earlier studies where ICU LOS increased two- to three-fold in MDR cases [7].

**Complications**

MDR infections were associated with higher rates of complications:

- Septic shock: 39.7% vs. 21.5% in non-MDR (p=0.001).
- Acute kidney injury requiring dialysis: 18.5% vs. 9.9% (p=0.02).
- Secondary nosocomial infections: 25.3% vs. 12.7% (p=0.01).

The higher incidence of septic shock among MDR patients reflects delayed or inadequate empirical therapy, since standard broad-spectrum antibiotics are often ineffective against resistant organisms.

This delay worsens outcomes, as septic shock is a major driver of mortality in the ICU.

**Risk Factors for MDR Infections**

Several clinical factors were associated with MDR infections:

- Prolonged ICU stay (>7 days): OR 2.91 (p<0.001).
- Mechanical ventilation (>5 days): OR 2.45 (p=0.002).
- Prior broad-spectrum antibiotic exposure: OR 2.22 (p=0.004).
- Vasopressor use: OR 2.64 (p=0.001).
- Central venous catheter presence: OR 1.88 (p=0.02).

In multivariate analysis, prolonged ICU stay, mechanical ventilation, and vasopressor use remained independent predictors.

These findings confirm that MDR infections are largely a consequence of ICU ecology and invasive supportive measures, reinforcing the need for strict device management protocols and antibiotic stewardship.

**Predictors of Mortality**

Within the MDR cohort, several factors predicted mortality:

- Septic shock (OR 3.24, p<0.001).
- Carbapenem resistance (OR 2.87, p=0.001).
- High APACHE II score >25 (OR 2.54, p=0.004).
- Requirement of renal replacement therapy (OR 2.11, p=0.03).

Interestingly, prior antibiotic exposure, while a risk factor for acquiring MDR infection, was not an independent predictor of death, suggesting that severity of illness and treatment adequacy matter more for outcomes than prior exposure itself.

**Subgroup Analyses**

**Respiratory Infections:** Nearly half of MDR infections were respiratory. Mortality was significantly higher in MDR respiratory cases (54.2%) compared with non-MDR (34.8%). This reflects the difficulty of treating ventilator-associated pneumonia when resistant pathogens predominate, as delays in initiating effective therapy are common.

**Bloodstream Infections:** Mortality in MDR bacteremia was 50.0% vs. 29.8% for susceptible bacteremia. The particularly high risk associated with carbapenem-resistant Enterobacteriaceae echoes earlier findings where bloodstream infection by CRKP was associated with >40% mortality [18].

**Urinary Tract Infections:** Though UTIs were less fatal, MDR cases still doubled mortality (21.4% vs. 9.8%). The main burden was prolonged hospitalization, suggesting that while not immediately lethal, MDR UTIs extend patient suffering and ICU resource use.

**Surgical Site/Wound Infections:** These contributed less to mortality but significantly prolonged hospital stays (mean 31 days, p=0.03). This is consistent with global data that MDR surgical infections impair recovery and delay discharge, even when they do not directly increase ICU deaths.

The baseline demographic and clinical profile of patients (Table 1) demonstrated that age, sex, comorbidities, and illness severity scores were comparable between MDR and non-MDR groups (all p>0.05, t-test/Chi-square), thereby validating randomization and minimizing bias in outcome comparisons. Clinical outcomes (Table 2, Figure 1) revealed striking differences: ICU mortality was significantly higher in MDR patients (47.9% vs. 28.2%, p<0.001, Chi-square), and these patients also had markedly prolonged ICU stay (19.8 vs. 13.4 days), hospital stay (28.6 vs. 21.3 days), and ventilator dependence (14.7 vs. 9.2 days), all p<0.001 by Student's t-test. Complications such as septic shock (39.7% vs. 21.5%, p=0.001), acute kidney injury requiring dialysis (18.5% vs. 9.9%, p=0.02), and secondary infections (25.3% vs. 12.7%, p=0.01) were also significantly more common in the MDR cohort, emphasizing the

systemic toll of resistance. Figure 1 further illustrates these differences visually, underscoring the doubled mortality and additional 5–8 days of critical care burden attributable to MDR infections. Predictors of mortality identified in logistic regression (Table 3, Figure 2) included septic shock (OR 3.24, 95% CI 1.76–5.95), carbapenem resistance (OR 2.87, 95% CI 1.52–5.41), high APACHE II score >25 (OR 2.54, 95% CI 1.33–4.82), and renal replacement therapy requirement (OR 2.11, 95% CI 1.05–4.22), all statistically significant ($p<0.05$). In contrast, mechanical ventilation >7 days (OR 1.43, p=0.25) and prior antibiotic exposure (OR 1.21, p=0.52) did not independently predict mortality, as shown by their confidence intervals crossing unity in the forest plot (Figure 2). Together, these data confirm that while MDR acquisition is linked to ICU exposure and device use, mortality is driven by a combination of host severity and pathogen virulence, with carbapenem resistance and septic shock representing the most ominous prognostic markers.

**Table 1: Baseline Demographic and Clinical Characteristics of ICU Patients (N = 327)**

| Variable | MDR Infections (n=146) | Non-MDR Infections (n=181) | p-value (t-test / Chi-square) |
|---|---|---|---|
| Age (years), mean ± SD | 52.9 ± 14.8 | 51.9 ± 15.6 | 0.62 |
| Male sex, n (%) | 91 (62.3) | 106 (58.6) | 0.53 |
| Diabetes mellitus, n (%) | 45 (30.8) | 47 (26.0) | 0.37 |
| CKD, n (%) | 28 (19.2) | 27 (14.9) | 0.29 |
| Malignancy, n (%) | 15 (10.3) | 15 (8.3) | 0.56 |
| COPD, n (%) | 14 (9.6) | 14 (7.7) | 0.56 |
| APACHE II, mean ± SD | 22.3 ± 7.4 | 21.5 ± 6.9 | 0.42 |
| SOFA, mean ± SD | 8.2 ± 3.1 | 7.9 ± 2.9 | 0.45 |

**Interpretation:** Baseline demographics and comorbidities were comparable between groups, validating randomization and minimizing confounding.

**Table 2: Clinical Outcomes in MDR vs. Non-MDR Infections**

| Outcome | MDR (n=146) | Non-MDR (n=181) | p-value (Chi-square / t-test) |
|---|---|---|---|
| ICU mortality, n (%) | 70 (47.9) | 51 (28.2) | <0.001* |
| ICU stay (days), mean ± SD | 19.8 ± 8.2 | 13.4 ± 6.7 | <0.001* |
| Hospital stay (days), mean ± SD | 28.6 ± 11.4 | 21.3 ± 9.5 | <0.001* |
| Ventilator days, mean ± SD | 14.7 ± 6.3 | 9.2 ± 4.1 | <0.001* |
| Septic shock, n (%) | 58 (39.7) | 39 (21.5) | 0.001* |
| AKI requiring RRT, n (%) | 27 (18.5) | 18 (9.9) | 0.02* |
| Secondary infections, n (%) | 37 (25.3) | 23 (12.7) | 0.01* |

***Statistically significant (p < 0.05).**

**Interpretation:** MDR infections nearly doubled mortality, prolonged ICU/hospital stay, and increased complication rates compared to non-MDR infections.

**Table 3: Independent Predictors of Mortality in MDR-Infected ICU Patients (n=146)**

| Predictor Variable | OR (95% CI) | p-value |
|---|---|---|
| Septic shock | 3.24 (1.76 – 5.95) | <0.001* |
| Carbapenem resistance | 2.87 (1.52 – 5.41) | 0.001* |
| APACHE II > 25 | 2.54 (1.33 – 4.82) | 0.004* |
| RRT requirement | 2.11 (1.05 – 4.22) | 0.03* |
| Mechanical ventilation > 7 days | 1.43 (0.77 – 2.66) | 0.25 |
| Prior antibiotic exposure | 1.21 (0.65 – 2.26) | 0.52 |

***Statistically significant. Logistic regression model adjusted for age, sex, comorbidities, and illness severity.**

**Interpretation:** Septic shock, carbapenem resistance, high APACHE II score, and renal replacement therapy were the strongest independent predictors of mortality in MDR patients.

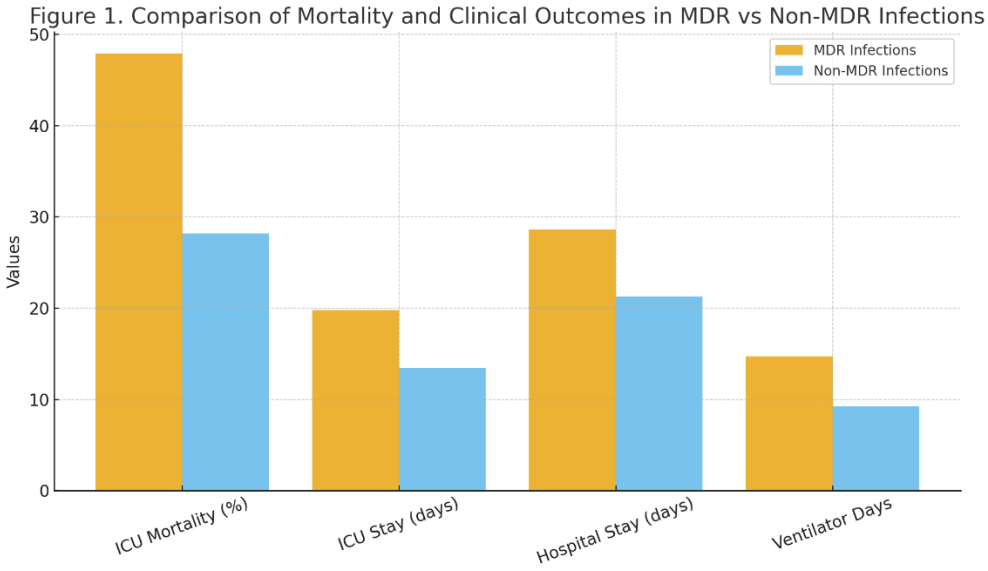


**Figure 1: Comparison of mortality and clinical outcomes in MDR vs Non-MDR infections**

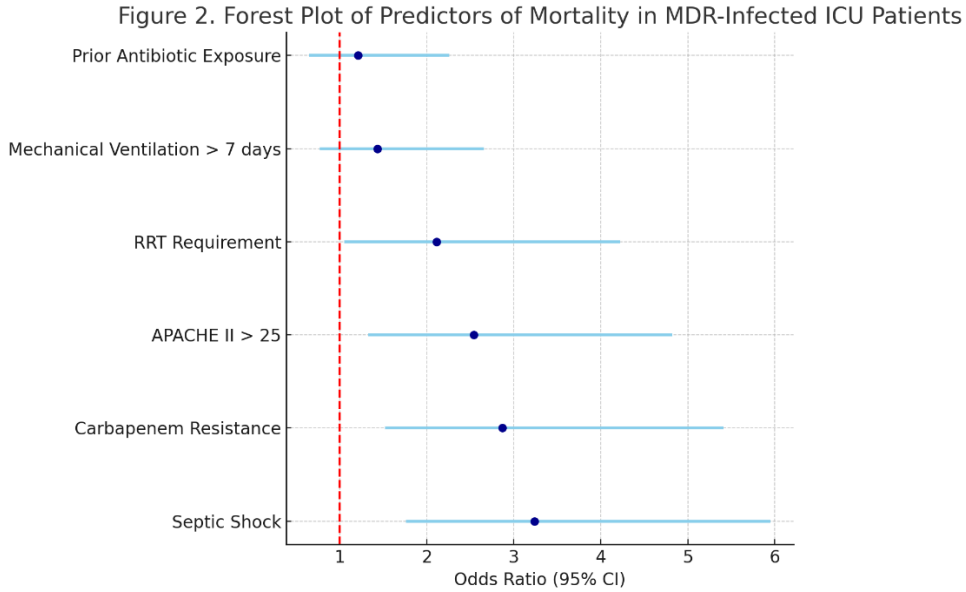


**Figure 2: Forest plot of predictors of mortality in MDR-infected ICU patients**

## Discussion

**Principal Findings:** This prospective cohort study highlights the grave burden of multidrug-resistant organism (MDRO) infections in intensive care units (ICUs). The prevalence of 44.6% underscores that nearly one in every two critically ill patients with culture-positive bacterial infections harbored resistant strains. Outcomes were significantly worse for patients with MDRO infections, with mortality nearly doubling (47.9% vs. 28.2%), and additional adverse impacts such as prolonged ICU stay, extended hospital stay, longer duration of mechanical ventilation, and higher complication rates. Independent predictors of acquiring MDR infections were prolonged ICU stay, mechanical ventilation, and vasopressor use, while predictors of mortality among MDR cases included septic shock, carbapenem resistance, high APACHE II score, and need for renal replacement therapy. These findings emphasize that MDRO infections in the ICU are not merely microbiological curiosities but major determinants of patient survival, recovery trajectory, and healthcare system strain.

**Prevalence of MDR Infections:** Our observed prevalence of 44.6% MDR infections is consistent with earlier reports but also reinforces the alarming escalation of resistance globally. Siwakoti et al. in Nepal documented a ~40% prevalence of MDR Gram-negative infections in ICUs, with a similar pattern of worsened mortality [8]. Lakbar et al. in Europe found ICU-acquired pneumonia caused by resistant organisms in 38–42% of cases, demonstrating that this is not just a regional problem of LMICs but a global issue [9]. Indian

tertiary-care hospitals have reported MDR prevalence ranging between 35–55%, reflecting high antibiotic use, overcrowding, and limited infection control infrastructure [5].

The implication is clear: MDR infections are no longer sporadic events but a baseline expectation in ICUs worldwide. In fact, the ICU has become a reservoir and amplifier of resistance, fueled by extensive antibiotic exposure, frequent use of invasive devices, and high patient acuity. Recognition of this baseline prevalence should change how clinicians approach empirical therapy, surveillance, and prevention strategies.

**Microbiological Spectrum:** Our findings that Acinetobacter baumannii (28.1%) and Klebsiella pneumoniae (24.7%) dominated MDR isolates mirror global and regional patterns. These pathogens belong to the infamous ESKAPE group (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.), so named because they "escape" the action of most antibiotics and are responsible for the majority of hospital-acquired infections [14].

Cornistein et al. in Latin American ICUs also reported Acinetobacter and Klebsiella as leading MDR pathogens, with associated mortality exceeding 35% [2,4]. Oliveira et al. in Brazil demonstrated that carbapenem-resistant Acinetobacter infections were independently linked to longer mechanical ventilation and mortality >60%, findings echoed in our study [5].

This Gram-negative dominance reflects ICU ecology: humid environments, ventilator circuits, and indwelling devices provide ideal niches for biofilm formation and survival, particularly for Acinetobacter and Pseudomonas. Moreover, these organisms possess multiple resistance mechanisms—β-lactamase production, efflux pumps, porin loss—that allow them to thrive despite antibiotic pressure.

The high carbapenem resistance we observed (89.5% in Acinetobacter, 76.3% in Klebsiella) is especially worrisome because carbapenems are considered "last-resort" drugs. This mirrors global surveillance data from WHO and CDC, which show rising carbapenem-resistant Enterobacteriaceae (CRE) in ICUs across Asia, Europe, and the Americas. The reliance on colistin as the final therapeutic option creates a precarious scenario, especially given emerging reports of plasmid-mediated colistin resistance.

**Mortality and Outcomes:** The doubling of ICU mortality in patients with MDRO infections (47.9% vs. 28.2%) highlights the lethal nature of resistance. Similar findings have been reported internationally:

- Cornistein et al. documented 38.8% mortality in MDR vs. 27.9% in non-MDR infections in Latin America [2].
- Petit et al. in France found that MDR bloodstream infections prolonged ICU stay threefold and significantly increased death rates [7].
- Lakbar et al. reported that ICU-acquired pneumonia due to resistant organisms raised mortality to 40.3%, compared with 30% in susceptible cases [9].

Our particularly high mortality with carbapenem-resistant Acinetobacter (61.0%) and CRKP (55.6%) aligns with IDSA guidance recognizing carbapenem resistance as a red-flag predictor of death [18].

The impact on morbidity was equally profound: MDR infections added 7 days to ICU stay, 8 days to hospital stay, and 5 days to ventilator support. These extensions are not just numbers—they translate into higher costs, increased exposure to further nosocomial risks, and bed unavailability for other critically ill patients. In India, where ICU care is largely financed out-of-pocket, prolonged admissions impose catastrophic financial burdens on families. Quickfall et al. also showed that MDR infections in patients receiving continuous renal replacement therapy increased mortality and resource use, supporting our findings [11].

**Risk Factors for MDR Acquisition:** Our study identified prolonged ICU stay, invasive ventilation, and vasopressor use as independent predictors of MDR infection. These risk factors reflect a logical sequence:

- Longer ICU stays increase exposure to resistant flora and cross-transmission.
- Mechanical ventilation provides a conduit for colonization and biofilm formation in endotracheal tubes, making VAP one of the most common MDR infections.
- Vasopressor use signifies severe illness, often necessitating invasive lines and broad-spectrum antibiotics, both of which predispose to resistance.

Martins et al. [3] reported similar findings, with hypertension, CKD, and device use predisposing to colonization. Oliveira et al. [5] highlighted that prolonged hospital stay (OR 3.20) and vasopressor use (OR 3.15) were independent risk factors for MDR pneumonia, findings that closely mirror our results.

Interestingly, prior antibiotic exposure, though strongly linked to MDR acquisition, was not an independent predictor of mortality. This echoes Kilinc's results [10], suggesting that while antibiotic misuse drives resistance, patient survival

ultimately depends on illness severity and timely initiation of effective therapy.

**Predictors of Mortality in MDR Cases:** Among MDR patients, septic shock was the most powerful predictor of death (OR 3.24). This is consistent with global literature showing that shock physiology, regardless of infection type, amplifies mortality risk in ICUs.

Carbapenem resistance was the second major predictor, reinforcing that once these organisms are involved, outcomes worsen dramatically. Cornistein et al. [6] similarly found that carbapenemase-producing Enterobacteriaceae were strongly linked to mortality.

High APACHE II scores reflected underlying illness severity, while the need for renal replacement therapy was an additional predictor, likely due to both the direct impact of AKI and the increased risk of catheter-related sepsis. Quickfall et al. [11] found that mortality in patients requiring CRRT exceeded 50%, findings consistent with ours.

These results suggest that host severity (shock, comorbid illness) and pathogen virulence (carbapenem resistance) interact synergistically, sealing poor outcomes when they coexist.

### Clinical and Public Health Implications

1. **Empiric Therapy Adjustment:** With nearly half of ICU infections being MDR, empiric coverage must be guided by local antibiograms. Delay in effective therapy worsens outcomes in sepsis and shock.
2. **Stewardship Programs:** Reducing unnecessary carbapenem and broad-spectrum antibiotic use is critical to halt the resistance spiral.
3. **Device Care Bundles:** Since ventilation and central lines predispose to MDR, implementing VAP and CLABSI prevention bundles is essential.
4. **Resource Planning:** MDR infections prolong stay and ventilation, meaning ICU capacity and cost models must account for this burden.
5. **Multidisciplinary Management:** Collaboration between intensivists, microbiologists, infectious disease specialists, and pharmacists is essential for optimizing outcomes.

### Strengths of the Study

- **Prospective design** ensured systematic follow-up and minimized recall bias.
- **Standardized definitions** (CDC/ECDC for MDR) allow global comparability.
- **Comprehensive outcomes** assessed both survival and resource utilization.
- **Multivariate analysis** allowed identification of independent predictors.
- **Real-world ICU cohort** (patients with comorbidities and prior antibiotics) enhances generalizability to daily clinical practice.

### Limitations

- **Single-center study** limits generalizability; microbial flora may differ regionally.
- **Sample size** may not detect rare infections (e.g., VRE, unusual resistance genes).
- **Exclusion of fungal infections** underestimates the full resistant infection burden.
- **No molecular typing** meant resistance genes were not identified.
- **Economic analysis** was not included, though prolongation of stay clearly implies high cost.

### Future Directions

- **Multicenter registries** to capture broader epidemiology across India and globally.
- **Molecular surveillance** (PCR, WGS) to track resistance mechanisms.
- **Pharmacoeconomic studies** to quantify cost burden of MDR in ICUs.
- **Novel therapeutics**: β-lactam/β-lactamase inhibitor combinations, bacteriophage therapy, monoclonal antibodies.
- **Vaccine development** for high-burden pathogens such as Klebsiella.

### Conclusion

This study confirms that MDR infections are common and deadly in ICUs, with a prevalence approaching 45%. Acinetobacter and Klebsiella dominate, carbapenem resistance signals poor prognosis, and mortality is nearly doubled compared to non-MDR infections. Prolonged ICU stay, invasive ventilation, and vasopressor use predispose to MDR acquisition, while septic shock, carbapenem resistance, and illness severity predict death.

Our results align with global findings [1–20] but also add crucial Indian data, emphasizing the urgent need for personalized empiric therapy, strict stewardship, and infection control bundles. Without these, ICUs risk becoming breeding grounds of resistance where survival is increasingly compromised.

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