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Original Research Article

# Comparison of Clinical Outcomes in Sepsis Caused by Multidrug-Resistant (MDR) and Non-MDR *Klebsiella pneumoniae*

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**Abstract**

**Background**: *Klebsiella pneumoniae* is a common pathogen causing sepsis and is associated with high morbidity and mortality. The emergence of multidrug-resistant organisms (MDROs), particularly extended-spectrum β-lactamase-producing K. *pneumoniae* (ESBL-KP) and carbapenem-resistant *K. pneumoniae* (CRKP), has limited antimicrobial therapy options and may worsen clinical outcomes such as mortality and length of hospital stay (LOS).

**Objective**: This study aims to compare the clinical characteristics and outcomes of sepsis caused by multidrug-resistant *K. pneumoniae* and non-MDR strains, focusing on mortality and LOS.

**Methods**: An observational analytical study with a cohort design was conducted at Dr. M. Djamil General Hospital in Padang from October 2024 to January 2025. Subjects diagnosed with sepsis due to pneumonia and confirmed positive for *K. pneumoniae* through blood or respiratory cultures were included using consecutive sampling. Isolates were categorized into MDR (ESBL-KP and CRKP) and non-MDR. Clinical data were analyzed descriptively to describe subject characteristics, while bivariate analysis (*chi-square* and *independent t-test*) evaluated associations between resistance profiles and outcomes, focusing on mortality and LOS ($p$<0.05).

**Results**: In the study cohort of 70 subjects, 55.7% had confirmed infection with MDR strains and 44.3% with non-MDR. Mortality was highest in patients with CRKP (56.5%), followed by non-MDR (38.7%) and ESBL-KP (25.0%). Statistical analysis revealed a notable association between the resistance profiles of *K. pneumoniae* and mortality, with CRKP-infected patients showing a higher risk of death compared to non-MDR strains (RR=1.840; 95% CI:1.59–2.14, $p$<0.05). However, there were no statistically significant differences in mean hospital LOS across the groups (CRKP:16.30±9.81 days; ESBL-KP:13.63±9.77 days; non-MDR:16.06±9.49 days; all p>0.05).

**Conclusion**: Sepsis caused by multidrug-resistant *K. pneumoniae*, including CRKP strains, is significantly associated with increased mortality. Although no significant difference in LOS was observed between the groups, antimicrobial resistance was more strongly associated with mortality than with duration of hospitalization.

**Keywords**: *Sepsis; Klebsiella pneumoniae; multidrug-resistant; mortality; length of stay.*
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## INTRODUCTION

The rise of multidrug-resistant organisms (MDROs) poses a major global health threat. These pathogens resist multiple antibiotic classes, complicating treatment efforts. According to WHO, MDROs account for over 25% of hospital-acquired infections worldwide, affecting both hospitals and communities. Multidrug-resistant *Klebsiella pneumoniae*, particularly extended-spectrum β-lactamases (ESBLs) and carbapenemase-producing strains, has become a prominent cause of healthcare-associated infections (HAIs).[1,2] In 2024, the WHO classified carbapenem-resistant and ESBL-producing pathogens, including *K. pneumoniae*, as critical priority threats due to their limited treatment options and substantial effects on healthcare systems.[3]

The prevalence of carbapenem-resistant *K. pneumoniae* (CRKP) has increased globally, rising from 20.5% of bloodstream isolates in 2017 to 31.1% in 2023.[4] Local data from Dr. M. Djamil General Hospital in Padang showed that *K. pneumoniae* was the most common pathogen causing MDR infections in sepsis patients, accounting for 27.7% of cases, predominantly involving ESBL and carbapenem-resistant strains.[5] This trend has been linked to antibiotic overuse, disruptions caused by the COVID-19 pandemic, and lapses in infection control.[6] *K. pneumoniae* is a Gram-negative, encapsulated bacillus that normally colonizes the gut but can cause pneumonia, urinary tract infections, and sepsis, especially in hospitalized or immunocompromised individuals.[7,8] Pathogenic potential increases due to environmental persistence, colonization of medical devices, and transmission via healthcare workers.[8] The rising incidence of MDRO intensifies the urgency of addressing MDR sepsis, making it a crucial concern for global health.[2,3]

*K. pneumoniae* exhibits resistance to major antibiotic classes, including carbapenems, cephalosporins, aminoglycosides, and fosfomycin, often resulting in treatment failure. Resistance mechanisms include enzymatic inactivation (e.g., ESBLs, AmpC, and carbapenemases like *K. pneumoniae* carbapenemases (KPC), New Delhi metallo-β-lactamase (NDM), and oxacillinase-48-type carbapenemases (OXA-48), altered target binding, porin mutations, efflux pump overexpression, and biofilm formation. Many of these determinants are plasmid-mediated, enabling rapid horizontal gene transfer.[9] New resistance mechanisms worsen the challenge of treating infections, necessitating rapid and targeted therapy.[10]

Infections with MDR strains are often linked to higher morbidity, mortality, prolonged hospitalization, and increased healthcare costs.[11] In sepsis, MDR *K. pneumoniae* infections are associated with increased rates of organ dysfunction, delayed initiation of appropriate therapy, and significantly higher mortality compared to non-MDR strains. A study in Vietnam reported 10.8% mortality and 13.7% septic shock in patients with community-acquired sepsis caused by *K. pneumoniae*, with 87% resistance to ampicillin.[12] In intensive care unit (ICU) cohorts, MDR infections are consistently associated with longer ICU stays and higher 30-day mortality.[4,11] A study from Dr. M. Djamil General Hospital in Indonesia supports this concern. Fadrian et al. (2024) analyzed 5,539 samples collected before, during, and after the COVID-19 pandemic. MDRO rates, especially CRKP and extended-spectrum β-lactamase-producing *K. pneumoniae* (ESBL-KP), increased significantly. CRKP incidence was 1.94 times higher during the pandemic and 2.79 times higher after, compared to the pre-pandemic period. Sensitivity to key antibiotics such as amikacin, tigecycline, and cefepime also declined.[13] Previous research conducted at Dr. M. Djamil General Hospital Padang focused on antimicrobial resistance patterns, MDRO incidence, and antibiotic sensitivity trends before, during, and after the COVID-19 pandemic across the overall patient population. However, that study did not evaluate the clinical impact of resistance profiles on patient outcomes, specifically in patients with sepsis caused by pneumonia. Therefore, the present study aimed to assess the association between *Klebsiella pneumoniae* resistance profiles in pneumonia-related sepsis and clinical outcomes, specifically in-hospital mortality and length of stay (LOS).[13]

Specific initial empirical therapy incompatibility is associated with a death rate nearly twice as high in MDR sepsis patients compared to those with non-MDR strains, particularly in resource-limited healthcare facilities. In addition, MDR *Klebsiella pneumoniae* accounts for two-thirds of all bloodstream infections (BSIs).[14] Given the clinical impact and rising resistance, comparing outcomes of sepsis caused by MDR and non-MDR *K. pneumoniae* is essential. These findings may help guide empirical therapy, strengthen infection control, and support antimicrobial stewardship programs.

## MATERIALS AND METHODS

### Study Design and Participants

This observational analytical study with a cohort design was conducted at Dr. M. Djamil General Hospital, Padang, from October 2024 to January 2025. Adult patients (≥18 years) with sepsis due to pneumonia caused by *K. pneumoniae* were enrolled using consecutive sampling.

Inclusion criteria were adult patients with sepsis defined by a Sequential Organ Failure Assessment (SOFA) score ≥2 and microbiological confirmation of *K. pneumoniae* from blood or sputum. Patients were excluded if cultures yielded no growth or if they were discharged prematurely at their own request. To ensure accurate identification of the causative pathogen: 1) Sputum cultures: Sputum samples were analyzed to identify *K. pneumoniae* at the primary site of infection (the lungs); 2) Blood cultures: Samples were collected to detect the presence of the pathogen in the circulatory system, confirming systemic dissemination from the respiratory source.

Sepsis was defined according to the Sepsis-3 criteria, whereby organ dysfunction is identified by an acute increase of two or more points in the total SOFA score from baseline, which is assumed to be zero in the absence of prior organ dysfunction, in the presence of confirmed infection. The SOFA score quantifies dysfunction across six organ systems (respiratory,

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coagulation, hepatic, cardiovascular, central nervous system [CNS], and renal), each scored on a scale from 0 to 4. Septic shock was defined as sepsis with persistent hypotension requiring vasopressors to maintain a mean arterial pressure of at least 65 mmHg, and a serum lactate level above 2 mmol/L, despite adequate fluid resuscitation.[15]

Pneumonia was categorized using Infectious Diseases Society of America (IDSA) guidelines which characterize pneumonia by the presence of new infiltrates on chest radiography accompanied by compatible clinical findings. These findings include fever, cough with or without purulent sputum, dyspnea, auscultatory findings such as crackles (wet rhonchi), and leukocytosis or leukopenia. Community-acquired pneumonia (CAP) referred to infections acquired outside the hospital or within 48 hours of admission without prior healthcare exposure. Hospital-acquired pneumonia (HAP) was defined as pneumonia developing 48 hours or more after admission and not present at admission.[16,17]

In this study, MDR was defined according to Magiorakos et al. as resistance to at least one agent in three or more different antimicrobial categories. This definition applies to a broad range of pathogens, including ESBL-producing Enterobacteriaceae, carbapenem-resistant *K. pneumoniae* (CRKP), and other Gram-negative and Gram-positive bacteria.[18]

After informed consent from the patient's family, clinical data were recorded prospectively. Collected variables included age, sex, comorbidities, infection source, SOFA score, empirical antibiotics, and laboratory results. Healthcare exposure factors were documented: urinary catheter, central venous catheter (CVC), nasogastric tube (NGT), and mechanical ventilation. Recent surgery during hospitalization, admission within 60 days, and referral from another facility were noted as MDR risk factors. Data were extracted from medical records using a standardized form by trained researchers.

**Microbiological Procedures**

Specimen collection was limited to blood and sputum. Blood cultures were obtained aseptically from two separate venipuncture sites and inoculated into BacT/ALERT bottles. Sputum was collected by spontaneous expectoration in alert patients and by sterile mucus extractor in unconscious patients to minimize saliva contamination and enable direct collection from the lower respiratory tract. All sputum samples were required to be of good quality and free from contamination. Good-quality sputum was characterized by thick, cloudy mucus and was subsequently included for further molecular analysis.[19] Additionally, Gram stain analysis was performed on each sample to assess cellular composition, with adequate specimens defined as having <10 epithelial cells and >25 leukocytes per low-power microscope field, ensuring that only sputum originating from the lower respiratory tract was processed. All specimens were promptly transported to the microbiology laboratory for analysis. Diagnosis was confirmed by positive blood or sputum cultures. Isolates were classified as MDR (ESBL-KP or CRKP) or non-MDR.

**Detection of ESBL and Carbapenem Resistance**

Identification and susceptibility testing of *K. pneumoniae* isolates were performed using the VITEK-2 Compact system (bioMérieux, France), an automated platform that applies colorimetric and fluorometric techniques to identify bacteria and assess antimicrobial susceptibility. Detection of ESBL and carbapenem resistance followed the instrument's standardized protocols, aligned with Clinical and Laboratory Standards Institute (CLSI) guidelines.[20] All procedures were performed according to standard microbiological protocols in the microbiology laboratory of Dr. M. Djamil General Hospital Padang.

**Empirical Therapy**

Empirical antibiotics were administered at sepsis onset, before susceptibility results were available. Selection of agents was guided by the hospital's local antibiogram data, prioritizing agents with known activity against *K. pneumoniae*. All isolates subsequently underwent susceptibility testing using the VITEK-2 Compact system to adjust therapy as needed based on confirmed resistance profiles.

**Statistical Analysis**

Subjects were observed continuously throughout their hospital stay, and outcomes, including in-hospital mortality and length of stay (LOS), were recorded until discharge or death. Univariate analysis was used to summarize baseline characteristics. The normality of LOS data was assessed and confirmed. Bivariate analysis was then performed: the *chi-square test* was used to evaluate the association between resistance profiles and mortality, while the *independent samples t-test* was applied to compare LOS between groups. All statistical analyses were conducted using SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

**Ethical Approval**

The study protocol received ethical clearance from the Research Ethics Committee of Dr. M. Djamil General Hospital, Padang (No: DP.04.03/D.XVI.XI/247/2024). Informed consent was obtained from all legal guardians, and data confidentiality was maintained in accordance with the Declaration of Helsinki.

## RESULTS

This study included 70 sepsis patients with *K. pneumoniae* infection. MDR strains were found in 55.7% (n=39), comprising 23 CRKP and 16 ESBL-KP cases. The remaining 44.3% (n=31) had non-MDR. (Table 1 and Table 2)

The majority of patients were male (67.1%) and over 60 years of age (71.4%). Most patients were treated in the high care unit (54.3%), followed by the ICU (28.6%) and general ward (17.1%). Septic shock was noted in 48.6% of cases, mainly in the MDR group (82.4% vs. 17.6% in non-MDR). Mean SOFA scores were similar between groups (15.52 ± 9.56 for MDR and 15.26 ± 9.30 for non-MDR). HAP occurred more in the MDR group (65.5%), while CAP was more common in the non-MDR (73.2%). Comorbid conditions were

**Table 1.** Demographic and Clinical Characteristics of Patients with Sepsis due to *Klebsiella pneumoniae*

| Characteristics | n = 70 (%) | MDR, n (%) | Non-MDR, n (%) | *p*-value | RR (95% CI) |
|---|---|---|---|---|---|
| Age | | | | | |
| 18-60 years | 20 (28.6) | 5 (25.0) | 15 (75.0) | 0.382 | 0.750 (0.439-1.280) |
| >60 years | 50 (71.4) | 20 (40.0) | 30 (60.0) | | |
| Gender | | | | | |
| Male | 47 (67.1) | 17 (36.2) | 30 (63.8) | 1.000 | 0.979 (0.630-1.521) |
| Female | 23 (32.9) | 8 (34.8) | 15 (65.2) | | |
| Care Unit | | | | | |
| Intensive care unit (ICU) | 20 (28.6) | 11 (55.0) | 9 (45.0) | 0.856 | N/A |
| High care unit (HCU) | 38 (54.3) | 25 (65.8) | 13 (34.2) | | |
| General Ward | 12 (17.1) | 3 (25.0) | 9 (75.0) | | |
| Septic Shock | | | | | |
| Yes | 34 (48.6) | 28 (82.4) | 6 (17.6) | 0.487 | 1.222 (0.799-1.870) |
| No | 36 (51.4) | 12 (33.3) | 24 (66.7) | | |
| SOFA Score (Mean ± SD) | 15.58 ± 9.57 | 15.52 ± 9.56 | 15.26 ± 9.30 | 0.663 | N/A |
| Infectious Disease Diagnosis, n (%) | | | | | |
| Community-acquired pneumonia (CAP) | 41 (58.6) | 11 (26.8) | 30 (73.2) | 0.001* | 0.193 (0.069–0.541) |
| Hospital-acquired pneumonia (HAP) | 29 (41.4) | 19 (65.5) | 10 (34.5) | 0.001* | 5.182 (1.847–14.534) |
| Empirical Antibiotic Therapy | | | | | |
| Ampicillin–Sulbactam | 48 (68.6) | 26 (54.2) | 22 (45.8) | 0.700 | 0.818 (0.294–2.274) |
| Cefepime | 14 (20.0) | 10 (71.4) | 4 (28.6) | 0.237 | 2.328 (0.652–8.309) |
| Ceftazidime | 7 (10.0) | 2 (28.6) | 5 (71.4) | 0.228 | 0.281 (0.051–1.562) |
| Cefoperazone–Sulbactam | 10 (14.2) | 7 (70.0) | 3 (30.0) | 0.495 | 2.042 (0.482–8.656) |
| Cefotaxime | 11 (15.7) | 3 (27.3) | 8 (72.7) | 0.572 | 1.318 (0.506–3.432) |
| Levofloxacin | 41 (58.6) | 24 (58.5) | 17 (41.5) | 0.580 | 0.382 (0.033–4.416) |
| Moxifloxacin | 3 (4.3) | 1 (33.3) | 2 (66.7) | 0.492 | 1.405 (0.532–3.708) |
| Meropenem | 28 (40.0) | 17 (60.7) | 11 (39.3) | 0.700 | 0.818 (0.294–2.274) |

MDR=Multidrug-Resistant; SOFA = Sequential Organ Failure Assessment.
** $p < 0.05$ (significant)*
*N/A: Data not available or not applicable for this category.*

common in the study population. Those with a single comorbidity made up 44.3% of the total sample, with 54.8% in the MDR group. Meanwhile, 34.3% had multiple comorbidities, and 66.7% of these were classified as MDR. The most prevalent comorbidities included diabetes mellitus (75%), malignancy (86.7%), and chronic kidney disease (83.3%), predominantly found in the MDR group.

The use of medical devices was prevalent in both the MDR and non-MDR. Urinary catheters were the most frequently used device, observed in 81.4% of all subjects, with slightly higher use in the non-MDR (61.4%) compared to the MDR group (38.6%). Mechanical ventilation was needed in 51.4% of patients, more frequently in the MDR strains (61.1%) compared to the Non-MDR (38.9%). Conversely, CVC use was higher in the MDR group, with 88% of placements occurring in these patients, while the non-MDR accounted for 12%. NGT were employed in 92.8% of cases, with 63.1% from the non-MDR and 36.9% from the MDR. Furthermore, patients in the MDR strains were more likely to have had recent surgeries (70.9% vs. 29.1%), prior hospitalizations within the last 60 days (76.9% vs. 23.1%), and referrals from other healthcare facilities (77.4% vs. 22.6%) when compared to the non-MDR (Table 2).

**Outcome Analysis**

Bivariate analysis showed a statistically significant association between resistance profile and in-hospital mortality. Subjects with CRKP had the highest mortality rate (56.5%), followed by non-MDR (38.7%) and ESBL-KP (25.0%) (Table 3). In pairwise comparisons, subjects with CRKP infection exhibited higher mortality than those with ESBL-KP (56.5% vs. 25.0%, RR = 0.399; 95% CI: 0.660–4.570 $p > 0.05$), although the difference was not statistically significant. Mortality in CRKP-infected patients was also higher

compared to non-MDR infections (56.5% vs. 38.7%, RR = 1.84; 95% CI: 1.59–2.14, $p < 0.05$). Despite the variation in mortality rates, the analysis of LOS revealed no statistically significant differences among the resistance groups (Table 4). The mean LOS was 16.30 ± 9.81 days for CRKP infections, 13.63 ± 9.77 days for ESBL-KP, and 16.06 ± 9.49 days for non-MDR cases. All pairwise comparisons showed $p > 0.05$.

## DISCUSSION

More than half of sepsis patients were infected with MDR strains, mainly CRKP and ESBL-KP. This finding reflects global trends of an increasing burden of MDR *Klebsiella pneumoniae*, particularly in critical care settings. A 2024 meta-analysis estimated global CRKP prevalence at 28.7%, with South Asia reporting the highest rate (66.04%) and North America the lowest (14%).[21] In Indonesia, a 2025 meta-analysis by Kadariswantiningsih et al. (2025) reported a pooled prevalence of 46.38% for ESBL-producing bacteria. *K. pneumoniae* represented 51.03% of these isolates. Sumatra showed the highest regional prevalence at 63.99%, consistent with findings from this study conducted at a referral hospital in West Sumatra.[22]

Most participants in this study were males over 60, reflecting established risk factors for severe sepsis and MDR infections. Aging causes immunosenescence, characterized by diminished innate and adaptive immune responses. This process involves reduced naive cell production, impaired cellular function, and disrupted inflammatory pathways. Collectively, these changes compromise pathogen clearance and increase susceptibility to severe infections, including sepsis.[23] Comorbidities are also more prevalent in older adults and further compromise immune defenses.[24] In this study, patients with MDR infections had at least one comorbidity, highlighting the impact of underlying conditions on MDR risk. Male sex has been associated with a higher risk of sepsis, possibly due to biological differences in sex hormones. Testosterone may suppress immune function, while estrogen appears to enhance it. Moreover, men typically have more chronic diseases and often engage in behaviors that raise infection risk.[25]

**Table 2.** Comorbidities and Clinical Risk Factors

| Variable | Total (n=70) | MDR | Non-MDR | *p*-value | RR (95% CI) |
|---|---|---|---|---|---|
| **Number of Comorbidities** | | | | | |
| >1 Comorbidity | 24 (34.3) | 8 (33.3) | 16 (66.7) | 0.002* | 0.077 (0.014–0.427) |
| 1 Comorbidity | 31 (44.3) | 17 (54.8) | 14 (45.2) | 0.049* | 0.187 (0.036–0.971) |
| No Comorbidity | 15 (21.4) | 13 (86.7) | 2 (13.3) | 0.007* | 0.128 (0.026–0.623) |
| **Type of Comorbidities, n (%)** | | | | | |
| Diabetes mellitus | 16 (22.9) | 12 (75.0) | 4 (25.0) | 0.364 | 0.754 (0.496-1.146) |
| Chronic kidney disease | 12 (17.1) | 10 (83.3) | 2 (16.7) | 0.072 | 0.600 (0.418-0.861) |
| Chronic lung disease | 9 (12.9) | 6 (66.7) | 3 (33.3) | 0.721 | 0.811 (0.484-1.360) |
| Chronic liver disease | 2 (2.9) | 1 (50.0) | 1 (50.0) | 1.000 | 1.118 (0.275-4.541) |
| Heart failure | 11 (15.7) | 9 (81.8) | 2 (18.2) | 0.744 | 0.852 (0.515-1.412) |
| Malignancy | 15 (21.4) | 13 (86.7) | 2 (13.3) | 0.615 | 1.247 (0.694-2.239) |
| **Use of medical devices** | | | | | |
| Urinary catheter | 57 (81.4) | 22 (38.6) | 35 (61.4) | 0.064 | 3.580 (0.982–13.042) |
| Mechanical ventilation | 36 (51.4) | 22 (61.1) | 14 (38.9) | 0.350 | 1.571 (0.608–4.060) |
| Central venous catheter (CVC) | 25 (35.7) | 22 (88) | 3 (12) | *0.001 | 12.078 (3.136-46.520) |
| Nasogastric tube (NGT) | 65 (92.8) | 24 (36.9) | 41 (63.1) | 1.000 | 0.828 (0.129-5.289) |
| **History of Recent Surgery** | | | | | |
| Yes | 31 (44.3) | 22 (70.9) | 9 (29.1) | 0.709 | 1.143 (0.743-1.756) |
| No | 39 (55.7) | 17 (43.6) | 22 (56.4) | | |
| **History of Hospitalization in the Past 60 Days** | | | | | |
| Yes | 26 (37.1) | 20 (76.9) | 6 (23.1) | 1.000 | 1.055 (0.680-1.637) |
| No | 44 (62.9) | 25 (56.8) | 19 (43.2) | | |
| **Referral from Another Healthcare Facility** | | | | | |
| Yes | 31 (44.3) | 24 (77.4) | 7 (22.6) | 0.709 | 1.143 (0.743-1.756) |
| No | 39 (55.7) | 11 (28.2) | 28 (71.8) | | |

* *$p < 0.05$ (significant)*

**Table 3.** Bivariate Analysis of MDR *Klebsiella pneumoniae* and Mortality (n = 70)

| Group | Died, n (%) | Survived, n (%) | *p-value* | RR (95% CI) |
|---|---|---|---|---|
| MDR CRKP vs Non-MDR | 13 (56.5%) vs 12 (38.7%) | 10 (43.5%) vs 19 (61.3%) | *0.049 | 1.840 (1.591-2.136) |
| MDR ESBL-KP vs Non-MDR | 4 (25.0%) vs 12 (38.7%) | 12 (75.0%) vs 19 (61.3%) | 0.539 | 0.646 (0.248-1.682) |
| CRKP vs ESBL-KP | 13 (56.5%) vs 4 (25.0%) | 10 (43.5%) vs 12 (75.0%) | 0.399 | 1.739 (0.660-4.570) |

ESBL-KP = ESBL-producing *K. pneumoniae*; CRKP = Carbapenem-resistant *K. pneumoniae*.
** $p < 0.05$ (significant)*

**Table 4.** Comparison of Length of Stay Between *Klebsiella pneumoniae* Resistance Groups

| Comparison | n1 | Mean ± SD (days) | n2 | Mean ± SD (days) | *p-value* |
|---|---|---|---|---|---|
| MDR ESBL-KP vs Non-MDR | 16 | 13.63 ± 9.77 | 31 | 16.06 ± 9.49 | 0.413 |
| MDR CRKP vs Non-MDR | 23 | 16.30 ± 9.81 | 31 | 16.06 ± 9.49 | 0.928 |
| MDR CRKP vs MDR ESBL-KP | 16 | 13.63 ± 9.77 | 23 | 16.30 ± 9.81 | 0.406 |

Although age and sex distributions were similar between MDR and non-MDR, septic shock was significantly more frequent in MDR cases. This is consistent with a study by Ciapponi et al. (2023) which reported higher rates of shock and mortality in MDR infections. The crude case fatality rate for MDR reached 45%. After adjustment, death odds nearly doubled compared to non-MDR infections (odds ratio [OR] 1.93, 95% CI: 1.58-2.37). Delayed appropriate empirical therapy further elevated mortality risk (OR 2.27, 95% CI: 1.44-3.56). The worse outcomes observed in CRKP infections in this study may result from both antimicrobial resistance and the presence of additional virulence factors, such as capsular polysaccharides and biofilm formation, which promote systemic inflammation, tissue damage, and rapid progression to organ failure and shock.[26,27]

The lungs serve as a common entry point for pathogens in sepsis, making respiratory infections a major cause of systemic inflammation and organ failure. Pneumonia represents one of the most frequent sources of sepsis, particularly among hospitalized and critically ill patients. In sepsis, inflammatory mediators, endothelial injury, alveolar damage, and impaired gas exchange collectively contribute to respiratory failure. This risk is amplified in patients with comorbidities, immunosuppression, or exposure to invasive procedures such as intubation and mechanical ventilation, which compromise respiratory barriers and facilitate infection.[28]

The high incidence of HAP among MDR cases reflects prolonged hospitalization, prior antimicrobial exposure, and frequent use of invasive devices.[29] The high rate of HAP in MDR cases is linked to recent healthcare exposure, with 76.9% of affected patients hospitalized within the previous 60 days. Hospital environments, particularly intensive care units, are high-risk settings due to extensive antibiotic use and increased potential for patient-to-patient transmission.[30] In this study, MDR patients were more likely to receive treatment in the ICU or high-care units. Central venous catheters (CVCs) were predominantly found in MDR patients compared to non-MDR patients, suggesting that invasive device use may act as a confounding variable. Consequently, the risk of MDR infection may be influenced not only by bacterial resistance but also by exposure to invasive devices. These devices promote biofilm formation and persistent bacterial colonization, raising the risk of HAP and subsequent MDR infections in sepsis. Additionally, invasive procedures like intubation and mechanical ventilation weaken respiratory defenses, facilitating pathogen entry.[31]

Patients with sepsis from MDR often present multiple comorbidities due to shared risk factors. Chronic conditions such as diabetes, chronic kidney disease, and cancer compromise immune defenses, increasing susceptibility to severe and recurrent infections with resistant bacteria. These patients also frequently receive broad-spectrum antibiotics, undergo invasive procedures, and experience prolonged hospital stays, elevating MDRO colonization and infection risk. Additionally, comorbidities contribute to extended hospitalizations, increased disease severity, and higher rates of HAIs and antimicrobial resistance.[32,33]

This study found a high prevalence of comorbidities among sepsis patients. A single comorbidity was identified in some cases, with more than half occurring in the MDR group. Multiple comorbidities were also observed, and most of these cases involved MDR infections. The most common comorbidities were diabetes mellitus, malignancy, and chronic kidney disease, particularly prevalent in the MDR group. Previous research at Dr. M. Djamil General Hospital in Padang showed that 75% of diabetic sepsis patients had MDR infections. Similarly, a study by Alsehemi et al. (2023) reported diabetes as the most frequent comorbidity (50%) among patients with MDR infections. Chronic illnesses also result in prolonged hospitalization, frequent antibiotic exposure, and the need for invasive procedures. These factors collectively increase the risk of colonization and infection. Therefore, early identification and effective management of comorbidities are essential to reduce the impact of MDR sepsis.[5,33,34]

In this study, patients with a history of recent surgery were more likely to be infected with MDR *K. pneumoniae*. Surgical procedures compromise natural

barriers and often involve the use of invasive devices, allowing resistant pathogens to enter the body. Inappropriate use of prophylactic antibiotics, including incorrect timing, suboptimal dosing, or unsuitable drug selection, may fail to prevent infections and instead encourage resistance. The perioperative use of broad-spectrum antibiotics also increases selective pressure, facilitating colonization by resistant organisms. Previous research has linked surgical interventions to higher MDR risk due to surgical stress and cumulative antibiotic exposure.[35,36]

Inter-facility transfers expose patients to varying antibiotic protocols and inconsistent infection control measures, increasing MDR acquisition risk. Additionally, inadequate communication about colonization status delays appropriate empirical therapy. A study by Ellingson et al. (2022) of 54 acute-care hospitals indicated that 72% had interfacility transfer communication (IFTC) protocols. Hospitals with these protocols reported fewer communication barriers. However, only 44% consistently communicated MDRO status during transfers, and protocol implementation varied significantly. The absence of standardized communication methods and unclear responsibilities for information transfer at receiving facilities are major challenges. These findings underscore the need for structured and coordinated IFTC systems to prevent the spread of MDROs and support effective antimicrobial stewardship.[37,38]

This study found that sepsis caused by multidrug-resistant *Klebsiella pneumoniae*, particularly CRKP, was associated with significantly higher mortality than non-MDR infections (56.5% vs. 38.7%, RR = 1.84; 95% CI: 1.59–2.14, $p < 0.05$). Mortality rates were highest in the CRKP group at 56.5%, followed by non-MDR at 38.7% and ESBL-KP at 25.0%. These results are consistent with a systematic review by Li et al. (2023) which showed CRKP infections had increased odds of death at all intervals: 7-day (OR 3.22; 95% CI 1.18–8.76), 14-day (OR 5.66; 95% CI 4.31–7.42), 28/30-day (OR 3.87; 95% CI 3.01–3.49), and in-hospital mortality (OR 4.05; 95% CI 3.38–4.85, *p*-value 0.04).[39] A separate study by Chen et al. (2024) on elderly patients identified CRKP infection (OR 2.35; 95% CI 1.92–3.06), malignancy, and higher SOFA scores as independent predictors of 90-day mortality.[40] Supporting these findings, a multicenter study in Latin America showed that carbapenem resistance increased mortality risk nearly threefold (OR 2.86; 95% CI 2.07–3.95) among Gram-negative infections.[26]

Carbapenem-resistant *K. pneumoniae* (CRKP) emergence results from diverse carbapenemase enzymes, including *K. pneumoniae* carbapenemases (KPC), New Delhi metallo-β-lactamase (NDM), Verona integron-encoded metallo-β-lactamase (VIM), imipenemase metallo-β-lactamase (IMP), and oxacillinase-48-type carbapenemases (OXA-48). This study demonstrates that CRKP-infected patients experience significantly higher rates of adverse outcomes, including extended hospitalization and septic shock. These poor outcomes correlate directly with disease severity as reflected by SOFA scores.[41,42]

ESBL-KP, despite being multidrug-resistant, showed lower mortality than non-MDR strains; however, the difference was not statistically significant ($p > 0.05$). This finding may have been influenced by selection bias or the limited sample size. This observation may reflect timely diagnosis and the use of empirical carbapenem therapy guided by local resistance data. Although ESBL-KP resists most β-lactams, its retained susceptibility to carbapenems may allow better outcomes when therapy is administered promptly. However, nosocomial ESBL-KP isolates have demonstrated increasing hypervirulence and greater antimicrobial resistance compared with community-acquired strains. Conversely, our finding of lower mortality in the ESBL-KP group contradicts the results reported by Li et al. (2023), who analyzed 37,915 patients and observed higher mortality in ESBL-KP bacteremia than in non-ESBL cases, with odds ratios of 1.82 (14-day), 1.57 (30-day), and 1.57 (in-hospital), underscoring the clinical threat of HAIs. Conversely, the higher mortality observed in the non-MDR group compared with ESBL-KP may have been influenced by clinical confounders, including late presentation, comorbidities, or initial underestimation of infection severity. These findings also underscore the need for further stratified analyses to account for variables such as host factors, source control, and timing of interventions.[26,39]

SOFA scores were elevated in both groups (MDR: 15.52 ± 9.56 vs non-MDR: 15.26 ± 9.30), reflecting severe multi-organ dysfunction. The SOFA assessment evaluates six organ systems, with increases ≥2 points predicting higher mortality risk. In MDR sepsis cases, particularly those involving CRKP and ESBL-KP, elevated scores typically result from delayed appropriate therapy, enhanced bacterial virulence, and severe complications. Although SOFA score differences between groups were not statistically significant, septic shock occurred markedly more frequently in MDR cases (82.4% vs 17.6%). Previous research has demonstrated that septic shock represents an independent risk factor for MDRO sepsis, with an odds ratio of 2.2 (95% CI: 1.3–3.7, $p = 0.002$), suggesting that MDR infections are associated with more severe hemodynamic instability and clinical deterioration.[15,43]

Sepsis follows a biphasic immune response: an initial hyperinflammatory phase with excessive cytokine release causing endothelial dysfunction and hypoperfusion, followed by an immunosuppressive phase marked by lymphopenia, reduced HLA-DR expression, and immune cell apoptosis that increases susceptibility to MDR infections. Risk factors include invasive procedures, prolonged broad-spectrum antibiotic exposure, and gut microbiota disruption. Although SOFA scores were comparable between groups, the higher incidence of septic shock in MDR cases suggests greater progression to immunoparalysis, underscoring the need for continuous SOFA monitoring and early MDR detection.[44,45]

Empirical antibiotic selection patterns in this study reveal significant therapeutic challenges in managing suspected MDR infections. Ampicillin-sulbactam emerged as the most frequently prescribed agent, with relatively balanced distribution between MDR and non-MDR. This pattern suggests suboptimal prescribing in high-risk MDR. D'Onofrio et al. (2021) demonstrated that ineffective empirical antimicrobial

therapy correlates with a five-fold reduction in survival among septic shock patients, emphasizing the critical nature of appropriate initial selection.[46] Supporting evidence shows that appropriate antibiotics were administered in only 80.1% of sepsis cases, with corresponding survival rates of 52% versus 10.3% for inappropriate therapy (OR 9.45; 95% CI 7.74-11.54).[47]

The preferential use of cefepime and cefoperazone-sulbactam in the MDR group indicates clinical recognition of resistance patterns. However, continued reliance on ampicillin-sulbactam for MDR cases highlights the need for improved risk stratification protocols. Inadequate therapy affects 10-40% of sepsis cases, with variability dependent on local pathogen prevalence and guideline adherence. A large retrospective analysis of 21,608 adults with bloodstream infections revealed that 19% received discordant therapy, independently increasing mortality risk (adjusted OR 1.46; 95% CI 1.28-1.66). Given that 77.4% of referred patients and 76.9% of those with recent hospitalization harbored MDR strains, integrating healthcare exposure history into selection algorithms becomes paramount. High-risk populations would benefit from early carbapenem or broad-spectrum β-lactam/β-lactamase inhibitor combinations. Considering meropenem utilization reached only 40% overall, expanded use in vulnerable cohorts could enhance clinical outcomes.[48,49] In this study, all patients received definitive antibiotic therapy guided by the results of culture and susceptibility testing once these results became available.

The bivariate analysis of hospital length of stay revealed no statistically significant differences among resistance groups, despite clear mortality disparities. Mean LOS was 13.63 ± 9.77 days for ESBL-KP, 16.30 ± 9.81 days for CRKP, and 16.06 ± 9.49 days for non-MDR cases (all comparisons $p > 0.05$). This finding contradicts existing literature demonstrating that MDR infections typically prolong hospitalization. A comparative study of CRKP versus carbapenem-susceptible *K. pneumoniae* found significantly extended LOS for CRKP patients (31 vs 24 days, $p < 0.001$), despite comparable mortality rates between groups (13.50% vs 10.55%, $p = 0.324$).[50] Similarly, research from Shanghai demonstrated that patients with MDR/carbapenem-resistant isolates experienced significantly longer total hospitalization and post-isolation stays compared to those with susceptible strains ($p < 0.001$).[51]

This apparent contradiction may arise from competing risk factors that complicate the interpretation of LOS in sepsis studies. MDR bacterial isolation correlates with elevated mortality rates (40.2% vs 23.1%, $p = 0.001$) and *functions* as an independent predictor of death (OR: 4.6; 95% CI: 2.0–10.6, $p < 0.001$).[43] Hospital length of stay reflects multifactorial influences, including disease severity, patient frailty, clinical complications, socioeconomic circumstances, and family support systems. Paradoxically, prolonged hospitalization itself introduces additional risks, including healthcare-associated infections and functional decline, which may influence discharge decisions and mortality outcomes in critically ill populations.[52]

Several factors may obscure the relationship between resistance patterns and LOS in this study. The relatively small sample sizes combined with high standard deviations limit statistical power to detect meaningful differences. Institutional factors such as discharge policies, ICU bed availability, and family decisions regarding end-of-life care can standardize hospitalization duration independent of bacterial resistance profiles. ESBL-KP infections typically respond favorably to carbapenems when identified promptly, potentially facilitating faster clinical recovery. This contrasts with CRKP infections, which necessitate complex antibiotic combinations and often exhibit delayed therapeutic responses. However, the absence of statistical significance across all comparisons underscores how multiple confounding variables can mask the true impact of antimicrobial resistance on healthcare resource. In critically ill sepsis patients, competing factors including disease severity, comorbidities, and institutional practices may overshadow resistance-specific effects on hospitalization duration.[43,52]

## CONCLUSION

This study demonstrates that sepsis caused by multidrug-resistant *K. pneumoniae*, particularly carbapenem-resistant strains, is significantly associated with higher mortality compared to non-MDR and ESBL-producing strains, although length of stay was not significantly different between groups. The elevated SOFA scores and higher rates of septic shock in MDR cases underscore their severe clinical impact and emphasize the need for early detection, rapid initiation of effective antimicrobial therapy, and strengthened infection control measures. Considering the predominance of healthcare-associated risk factors—including recent surgery, prior hospitalization, and interfacility transfers—targeted prevention strategies are essential. These findings underscore the urgent need for early MDR risk stratification, prompt optimization of empirical antibiotic therapy based on local resistance patterns, and proactive antimicrobial stewardship to reduce mortality and improve clinical outcomes in sepsis patients.

### Limitations

The relatively small sample size may limit statistical power and the generalizability of the findings to broader populations. Additionally, this study was conducted in a single tertiary-care hospital over a limited study period, which may have restricted the total number of eligible participants. Strict inclusion criteria and incomplete clinical or microbiological data further reduced the final sample size. This study did not include a multivariate analysis to control for potential confounding factors such as age, comorbidities, and history of invasive procedures. Therefore, the associations identified may still be influenced by variables that were not statistically controlled. The study did not stratify outcomes by sex-specific differences in resistance patterns, nor did it explore other potentially influential variables such as genetic determinants of virulence, timing of antibiotic administration, or source control measures. This study did not evaluate the effect

of the appropriateness and timing of definitive antibiotic therapy on mortality, which may represent a source of residual confounding. Future multicenter studies with larger cohorts are warranted to validate these results and provide a more comprehensive understanding of multidrug-resistant *Klebsiella pneumoniae* sepsis outcomes.

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