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# Beyond Chronological Age: Clinical Determinants and Geriatric Vulnerability of 30-Day Mortality in Older Adults with Carbapenem-Resistant Enterobacterales Bloodstream Infections

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## Abstract

**Objective:** Carbapenem-resistant Enterobacterales bloodstream infections (CRE-BSIs) are associated with increased mortality, particularly among older adults. This study aimed to evaluate clinical severity, treatment-related factors, and geriatric vulnerability parameters associated with 30-day mortality in patients aged ≥65 years.

**Materials and Methods:** Patients aged 65 and older who were diagnosed with a BSI caused by CRE between 2016 and 2025 were included in this retrospective cohort study. Demographic, clinical, microbiological, and treatment-related data were collected. Geriatric vulnerability was assessed using the Hospital Frailty Risk Score (HFRS), the Geriatric Nutritional Risk Index (GNRI), polypharmacy, and functional dependency. To determine the factors associated with 30-day mortality, a Cox regression analysis was performed.

**Results:** Of the 177 patients included in the study, the 30-day mortality rate was 35.6%. The multivariate analysis revealed that a higher Pitt Bacteremia Score [adjusted hazard ratio (HR) = 1.24, 95% confidence interval (CI) 1.12-1.37, $p < 0.001$], a higher HFRS score (aHR = 1.12, 95% CI 1.04-1.21, $p = 0.002$), and a delay in appropriate treatment (≥72 hours) (aHR = 2.01, 95% CI 1.25–3.24, $p = 0.004$) was independently associatedwith increased mortality. GNRI was inversely associated with mortality (aHR = 0.96, 95% CI 0.93–0.99, $p = 0.008$). Chronological age and antimicrobial treatment type were not independently associated with mortality in the multivariable analysis.

**Conclusion:** Mortality in older adults with CRE-BSIs may be largely explained by infection severity and biological vulnerability rather than chronological age. Frailty and impaired nutritional status appear to be important determinants of outcome, while delayed initiation of appropriate therapy remains a critical modifiable factor.

**Keywords:** Carbapenem-resistant Enterobacterales, bloodstream ınfections, frailty, mortality, aged

## Introduction

Carbapenem-resistant Enterobacterales (CRE) infections have become a significant public health concern on a global scale due to their increasing prevalence, limited treatment options, and high mortality rates. The Centers for Disease Control and Prevention (CDC) classifies CRE among urgent antimicrobial resistance threats, and current guidance from the Infectious Diseases Society of America highlights the substantial mortality burden associated with CRE bloodstream infections (CRE-BSIs) (1,2).

Older age is consistently associated with poor clinical outcomes, including an increased mortality rate, in patients with CRE-BSIs (3-5). Consistently, multicenter epidemiological studies from Türkiye have demonstrated that infections in this population are more frequently associated with more severe clinical presentation and an increased need for intensive care unit (ICU) admission (6).

However, chronological age alone may not adequately reflect biological vulnerability in older adults. Aging is a heterogeneous

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process, and clinical outcomes in older adults are influenced not only by age but also by multidimensional factors such as comorbidity burden, malnutrition, polypharmacy, functional dependency, and reduced physiological reserve. These factors are conceptualized within the framework of frailty, a syndrome characterized by increased vulnerability to stressors and poorer clinical outcomes, including infections (7-9).

Although several studies have investigated predictors of mortality in CRE-BSIs among older adults, most have primarily focused on infection severity and treatment-related variables. Whether geriatric vulnerability beyond chronological age influences outcomes in CRE-BSIs remains unclear. The objective of this study was to identify the factors associated with 30-day mortality in older adults with CRE-BSIs, with a particular focus on geriatric vulnerability that extends beyond a patient's chronological age.

## Materials and Methods

This retrospective observational study was conducted at a tertiary-care academic center. Patients aged 65 and over who were hospitalized between January 1, 2016, and December 31, 2025, and who were diagnosed with CRE-BSIs were screened for eligibility. Patients meeting these criteria were included in the study, whereas patients with polymicrobial bacteremia detected in blood cultures, patients with recurrent CRE-BSIs (only the first episode was considered), patients whose blood culture isolates were deemed contaminants, or patients with incomplete or inaccessible clinical data were excluded.

Demographic, clinical, microbiological, geriatric, and treatment-related data were retrospectively obtained from the hospital information management system. The following variables were collected: age, sex, and body mass index. The Charlson Comorbidity Index (10) was used to assess the comorbidity burden. Additional variables included immunosuppressive therapy, history of solid organ transplantation, and history of hematopoietic stem cell transplantation. Geriatric vulnerability was evaluated using the Hospital Frailty Risk Score (HFRS) (11), nutritional status using the Geriatric Nutritional Risk Index (GNRI) (12) and polypharmacy defined as the use of five or more medications, and functional dependency prior to hospitalization.

Clinical and infection-related variables included ICU acquisition, hospital length of stay prior to BSI, presence of sepsis or septic shock according to Sepsis-3 criteria (13), Pitt Bacteremia Score (PBS) (14), calculated on the day of blood culture collection, need for mechanical ventilation, and source of infection defined according to CDC criteria (15).

Blood culture specimens were processed using the BacT/ALERT 3D system (bioMérieux, Craponne, France) according to standard laboratory protocols. Following a positive result, samples were subjected to Gram staining and then inoculated onto appropriate culture media. The inoculated plates were incubated at 37 °C for 24-48 hours for microbial growth. Bacterial identification was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Antimicrobial susceptibility testing was carried out with automated systems (VITEK® 2, bioMérieux; or BD Phoenix®, Becton Dickinson), and the results were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing criteria (16).

CRE-BSIs was defined as the isolation of an Enterobacterales strain showing non-susceptibility to at least one carbapenem agent from blood cultures (2). Frailty was evaluated using the HFRS, calculated based on ınternational classification of diseases, tenth revision (ICD-10) diagnostic coding (11). Because HFRS primarily reflects hospital-based frailty, additional parameters, including nutritional status, polypharmacy, and functional dependency, were evaluated to better capture multidimensional geriatric vulnerability. Nutritional status was assessed using the GNRI as described by Bouillanne et al. (12). Polypharmacy was defined as the regular use of at least five medications.

Treatment-related variables included empirical and targeted antimicrobial therapy and the time to initiation of appropriate therapy. Delayed targeted therapy referred to initiation of an antimicrobial agent with confirmed in vitro activity ≥72 hours after blood culture collection. Thirty-day mortality, defined as death within 30 days of the first positive blood culture, was used as the primary outcome.

Ethical approval was obtained from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval no: 416, date: 05.03.2026). The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice standards. Informed consent was not required due to the retrospective observational nature of the study.

### Statistical Analysis

Continuous variables were summarized as mean ± standard deviation or median interquartile range (IQR), depending on data distribution. Categorical variables are presented as counts and percentages. Group comparisons between survivors and non-survivors were performed using the Student's t-test or Mann-Whitney U test for continuous variables, and the chi-square or Fisher's exact test for categorical variables. No formal sample size calculation was performed due to the retrospective nature of the study. Missing data were handled using complete-case analysis. Univariable Cox proportional hazards regression was used to explore associations with 30-day mortality. Variables deemed clinically relevant or showing a p-value <0.10 were subsequently entered into the multivariable model. Collinearity was evaluated using the variance inflation factor (VIF), and variables with VIF >5 were excluded. The proportional hazards assumption was evaluated using Schoenfeld residuals and was met for all variables in the final model.

Survival probabilities were estimated using the Kaplan-Meier method, and group differences were compared with the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) are presented.

All statistical tests were two-sided, with a significance threshold of $p < 0.05$. P-values were reported in accordance with journal guidelines. Statistical analyses were conducted using IBM SPSS Statistics (version 29.0).

## Results

A total of 177 older adults with CRE-BSIs were included in the study. The median age was 74 years (IQR 68-81); 57.1% (n = 101) were male. No missing data were identified for variables used in geriatric vulnerability assessment, including HFRS, GNRI, polypharmacy, and functional dependency. During the 30-day follow-up, 63 patients (35.6%) died, while 114 (64.4%) survived. Although non-survivors tended to be older, the difference did not reach statistical significance. Baseline demographic, clinical, and microbiological characteristics are summarized in Table 1.

**Table 1. Baseline characteristics of geriatric patients with carbapenem-resistant Enterobacterales bloodstream infection according to 30-day mortality.**

| Variable | Overall, n = 177 (%)[1] | Survived, n = 114 (64.4%)[1] | Death, n = 63 (35.6%)[1] | p-value[2] |
|---|---|---|---|---|
| **Patient-related factors** | | | | |
| Age, median (IQR) | 74 (68-81) | 73 (67-80) | 76 (70-83) | 0.09 |
| Male sex, | 101 (57.1) | 63 (55.3) | 38 (60.3) | 0.52 |
| BMI, median (IQR) | 26.1 (22-30) | 26.4 (23-30) | 25.7 (21-31) | 0.41 |
| **Comorbidities** | | | | |
| CCI, median (IQR) | 5 (3-7) | 4 (3-6) | 7 (5-8) | <0.001 |
| Immunosuppressive therapy | 43 (24.3) | 20 (17.5) | 23 (36.5) | 0.006 |
| SOT | 14 (7.9) | 6 (5.3) | 8 (12.7) | 0.08 |
| HSCT | 10 (5.6) | 3 (2.6) | 7 (11.1) | 0.03 |
| **Geriatric vulnerability factors** | | | | |
| HFRS, median (IQR) | 7 (411) | 5 (39) | 11 (7-14) | <0.001 |
| GNRI, median (IQR) | 95 (88102) | 98 (92104) | 89 (83-95) | <0.001 |
| Polypharmacy ≥5 drugs | 98 (55.4) | 55 (48.2) | 43 (68.3) | 0.01 |
| Functional dependency | 66 (37.3) | 30 (26.3) | 36 (57.1) | <0.001 |
| **Clinical characteristics** | | | | |
| ICU-acquired BSI | 71 (40.1) | 36 (31.6) | 35 (55.6) | 0.003 |
| Length of hospital stay before BSI, days, median (IQR) | 10 (6-17) | 9 (6-15) | 12 (7-20) | 0.08 |
| Sepsis | 118 (66.7) | 66 (57.9) | 52 (82.5) | 0.001 |
| Septic shock | 39 (22.0) | 11 (9.6) | 28 (44.4) | <0.001 |
| PBS, median (IQR) | 4 (2-7) | 3 (1-5) | 7 (5-9) | <0.001 |
| Mechanical ventilation | 46 (26.0) | 18 (15.8) | 28 (44.4) | <0.001 |
| **Infection source** | | | | 0.64 |
| Primary BSI | 48 (27.1) | 30 (26.3) | 18 (28.6) | |
| UTI | 42 (23.7) | 29 (25.4) | 13 (20.6) | |
| Pneumonia | 39 (22.0) | 23 (20.2) | 16 (25.4) | |
| Catheter-related BSI | 21 (11.9) | 15 (13.2) | 6 (9.5) | |
| Intra-abdominal infection | 17 (9.6) | 11 (9.6) | 6 (9.5) | |
| SSTI | 10 (5.6) | 6 (5.3) | 4 (6.3) | |
| **Microbiological characteristics** | | | | 0.72 |
| *Klebsiella pneumoniae* | 109 (61.6) | 72 (63.2) | 37 (58.7) | |
| *Escherichia coli* | 34 (19.2) | 23 (20.2) | 11 (17.5) | |
| Other *Enterobacterales* spp. | 34 (19.2) | 19 (16.7) | 15 (23.8) | |

**Table 1. Continued.**

| Variable | Overall, n = 177 (%)[1] | Survived, n = 114 (64.4%)[1] | Death, n = 63 (35.6%)[1] | p-value[2] |
|---|---|---|---|---|
| **Treatment related characteristics** | | | | |
| Targeted therapy delay ≥72 h | 74 (41.8) | 33 (28.9) | 41 (65.1) | <0.001 |
| Targeted antimicrobial therapy | | | | 0.016 |
| - Polymyxin-based-regimen | 122 (68.9) | 71 (62.3) | 51 (81.0) | |
| - Ceftazidime-avibactam | 55 (31.1) | 43 (37.7) | 12 (19.0) | |

[1]Data are presented as n (%) or median interquartile range (IQR), 25th-75th percentiles [2]Statistical comparisons were performed using the chi-square test, Wilcoxon rank-sum test, or Fisher's exact test, as appropriate.
BMI: Body mass index, BSI: Bloodstream infections, CCI: Charlson Comorbidity Index, GNRI: Geriatric Nutritional Risk Index, HFRS: Hospital Frailty Risk Score, HSCT: Hematopoietic stem cell transplantation, ICU: Intensive care unit, IQR: interquartile range, PBS: Pitt Bacteremia Score, SOT: Solid organ transplantation, SSTI: Skin and soft tissue infection, UTI: Urinary tract infection.

Empirical antimicrobial therapy most frequently included carbapenems (37.3%, n = 66), followed by piperacillin-tazobactam (29.4%, n = 52), third-generation cephalosporins (21.5%, n = 38), and cefepime (11.9%, n = 21). No patients received ceftazidime-avibactam (CAZ-AVI) or polymyxin-based regimens during the empirical phase.

After susceptibility results became available, all patients were switched to targeted therapy: polymyxin-based regimens in 68.9% (n = 122) and CAZ-AVI in 31.1% (n = 55).

Table 2 summarizes the univariable Cox regression results. CAZ-AVI therapy was associated with lower mortality than polymyxin-based regimens (HR = 0.58, 95% CI 0.34-0.98, p = 0.04), whereas age was not a significant predictor of mortality.

A multivariable Cox model was constructed, including clinically relevant variables and those with $p < 0.10$ in the univariable analysis, namely infection severity (PBS), geriatric vulnerability (HFRS and GNRI), treatment delay, antimicrobial therapy type, and chronological age. Polypharmacy and functional dependency were excluded from the final model due to collinearity with the HFRS, as demonstrated by correlation analysis and the VIF.

In the adjusted model, higher PBS (aHR = 1.24, 95% CI 1.12-1.37, $p < 0.001$) and higher HFRS (aHR = 1.12, 95% CI 1.04-1.21, p = 0.002) were independently associated with increased mortality. In contrast, GNRI showed an inverse association with mortality (aHR = 0.96, 95% CI 0.93-0.99, p = 0.008); lower values, indicating poorer nutritional status, predicted higher mortality. Delayed initiation of appropriate targeted antimicrobial therapy (≥72 h) (aHR = 2.01, 95% CI 1.25-3.24, p = 0.004) significantly predicted mortality. Chronological age and antimicrobial treatment type were not independently associated with mortality after adjustment.

Survival was analyzed using the Kaplan-Meier method according to frailty status. Patients were categorized into three groups based on HFRS (low <5, intermediate 5-10, high >10). Thirty-day survival rates were 82%, 67%, and 41% for the low, intermediate, and high-frailty groups, respectively. Survival differed significantly across groups (log-rank $p < 0.001$). The corresponding survival curves are shown in Figure 1.

## Discussion

In this study, infection severity, frailty, nutritional status, and delayed initiation of appropriate therapy were associated with 30-day mortality in older adults with CRE-BSIs, whereas chronological age and antimicrobial treatment type were not. These findings suggest that prognosis in this population may be explained by biological vulnerability and acute illness severity rather than age alone.

Infection severity, as reflected by the PBS, was a strong independent predictor of mortality. This finding aligns with

**Table 2. Determinants of 30-day mortality identified by univariable and multivariable Cox regression.**

| Variable | Univariable HR (95% CI)[1] | p-value[2] | Multivariable aHR (95% CI)[1] | p-value[2] |
|---|---|---|---|---|
| Age (per year) | 1.02 (0.99-1.05) | 0.12 | 1.01 (0.98-1.04) | 0.31 |
| PBS (per point) | 1.31 (1.20-1.44) | <0.001 | 1.24 (1.12-1.37) | <0.001 |
| HFRS (per point) | 1.17 (1.09-1.26) | <0.001 | 1.12 (1.04-1.21) | 0.002 |
| GNRI (per point) | 0.95 (0.92-0.98) | <0.001 | 0.96 (0.93-0.99) | 0.008 |
| ≥72 h delay in targeted therapy | 2.47 (1.58-3.87) | <0.001 | 2.01 (1.25-3.24) | 0.004 |
| Ceftazidime-avibactam therapy* | 0.58 (0.34-0.98) | 0.04 | 0.69 (0.37-1.28) | 0.24 |

[1]95% confidence intervals (CIs) were calculated for hazard ratios. [2]p-values were derived from Cox proportional hazards regression models. *The reference category for antimicrobial therapy was a polymyxin-based regimen. Cox regression analyses were performed to assess predictors of 30-day mortality. Variables with clinical relevance or with p <0.10 were included in the multivariable model, whereas polypharmacy and functional dependency were excluded due to collinearity with HFRS.
HR: Hazard ratio, aHR: adjusted hazard ratio, CI: Confidence interval, PBS: Pitt bacteremia score (per point), HFRS: Hospital Frailty Risk Score (per point), GNRI: Geriatric Nutritional Risk Index (per point).

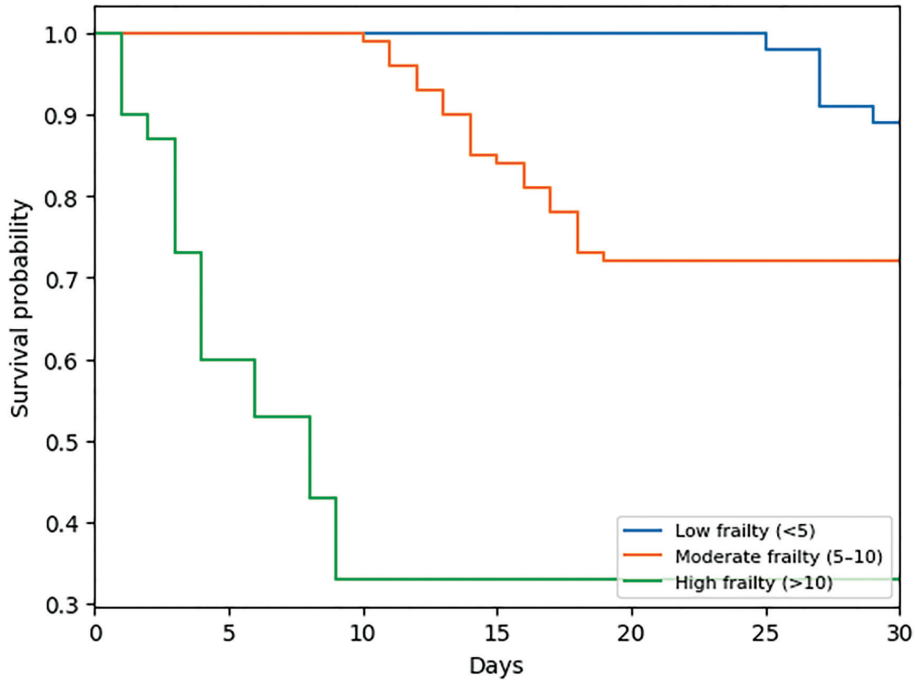


**Figure 1.** Kaplan-Meier survival analysis by HFRS frailty groups (log-rank $p < 0.001$).

*HFRS: Hospital Frailty Risk Score.*

previous studies showing that the severity of acute infection is a key determinant of outcomes in CRE-BSIs (3). Similar associations have been reported in older adult cohorts, where higher severity scores correlate with increased mortality (4,5). Overall, these results reinforce the central role of acute physiological derangement in determining prognosis.

Frailty, assessed using the HFRS, was also independently associated with mortality. Frailty is characterized by reduced physiological reserve and increased susceptibility to stressors, and is associated with adverse outcomes across a range of clinical settings (7-9). Our findings extend this concept to CRE-BSIs, suggesting that frailty is a critical determinant of outcomes beyond traditional infection-related parameters. Previous studies in infectious diseases have identified frailty as an independent predictor of mortality (17). These findings may support the integration of frailty assessment into the clinical evaluation of older adults with CRE-BSIs.

In addition to HFRS, nutritional status assessed by the GNRI was associated with mortality. Lower GNRI values, reflecting poorer nutritional status, were linked to a higher risk of death. This association is biologically plausible, as malnutrition impairs immune function and reduces the ability to respond to severe infections (12). These results highlight the role of nutritional vulnerability as a key component of geriatric risk stratification and support prior evidence linking malnutrition to adverse infection outcomes.

Although polypharmacy and functional dependency were more prevalent among non-survivors in descriptive analyses, they were excluded from the multivariable model because of collinearity with HFRS. Therefore, while these parameters likely reflect increased vulnerability, their independent contributions could not be established in this study.

Chronological age was not independently associated with mortality after adjustment. This finding underscores the heterogeneity of the older adult population and suggests that age alone is an insufficient marker of risk. Instead, parameters reflecting biological aging, such as frailty and nutritional status, appear to provide more meaningful prognostic information.

In univariable analysis, CAZ-AVI therapy was linked to lower mortality; however, this effect was not sustained after adjustment for confounders (18). This may reflect confounding by indication, as patients receiving polymyxin-based regimens likely had more severe disease. Therefore, the observed benefit may be attributable to differences in baseline characteristics rather than to a direct treatment effect.

Delayed initiation of appropriate targeted therapy remained an independent predictor of mortality, highlighting the importance of timely effective treatment in CRE-BSIs (2,3,19). However, this finding should be interpreted cautiously given the potential for immortal time bias inherent to retrospective time-to-treatment analyses. These findings also support the potential role of multidisciplinary approaches, including geriatric consultation

and antimicrobial stewardship programs, in facilitating earlier initiation of appropriate antimicrobial therapy in vulnerable older adults.

This study has several important strengths. It specifically addresses a high-risk geriatric population and incorporates a multidimensional assessment of vulnerability, including frailty, nutritional status, and infection-related parameters. This comprehensive approach provides a more nuanced understanding of factors influencing mortality in older adults with CRE-BSIs.

### Study Limitations

Several limitations should be acknowledged. First, the single-center retrospective design may limit generalizability and may be subject to residual confounding.

Second, although HFRS is a practical tool, it is retrospectively derived from ICD-10 coding data and may not fully capture all dimensions of frailty or provide real-time bedside clinical assessment during hospitalization (11). Therefore, prospective studies incorporating bedside frailty assessment tools such as the Clinical Frailty Scale may provide a more accurate evaluation of frailty and contribute more robust evidence to the literature.

Third, due to its real-world retrospective nature, molecular characterization of CRE isolates, including carbapenemase production and genotyping, could not be performed systematically, precluding evaluation of the impact of specific resistance mechanisms on outcomes. However, the inclusion of complementary parameters such as GNRI partially mitigates this limitation. Although time-to-event analysis was used, potential immortal time bias related to time-to-treatment variables cannot be fully excluded. Because patients classified as having delayed appropriate therapy were required to survive long enough to receive treatment after the predefined threshold, the magnitude of the observed association between treatment delay and mortality may have been overestimated.

## Conclusion

Mortality in older adults with CRE-BSIs appears to be influenced more by infection severity and biological vulnerability than by chronological age. Frailty and impaired nutritional status emerged as key determinants of outcome, while delayed initiation of appropriate therapy remained a critical modifiable risk factor. These findings support a shift from age-based to vulnerability-based risk assessment, emphasizing the need for early targeted treatment, multidisciplinary geriatric evaluation, and antimicrobial stewardship strategies to improve outcomes in this high-risk population.

### Ethics

**Ethics Committee Approval:** Ethical approval was obtained from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval no: 416, date: 05.03.2026). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

**Informed Consent:** Informed consent was waived due to the retrospective observational design of the study.

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### Footnotes

### Authorship Contributions

Surgical and Medical Practices: R.D., A.M., Concept: R.D., A.M., Design: R.D., A.M., Data Collection or Processing: R.D., Analysis or Interpretation: R.D., Literature Search: R.D., Writing: R.D., A.M.,

**Conflict of Interest:** No conflict of interest was declared by the authors.

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