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# Limited Impact of Colistin Resistance on Mortality of Intensive Care Patients with Carbapenem-resistant Bacteremia

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## SUMMARY

**Background.** Increasing incidence of carbapenem-resistant gram-negative bacteremias (CR-GNB) has triggered increased use of polymyxins, likely fueling the emergence and spread of colistin resistance.

**Aim.** To estimate the excess clinical burden of colistin resistance in intensive care patients with CR-GNB.

**Methods.** A cohort was constructed of patients with CR-GNB during their stay in the intensive care unit (ICU) of a University hospital in Greece, over a 4-year period (2020-2023). Competing risks survival analysis was performed to estimate the burden associated with colistin resistance.

**Findings.** In 177 ICU patients with CR-GNB, 134 (76%) had colistin-resistant isolates, predominantly *Acinetobacter baumannii* (79%), identified by broth microdilution. Patients with colistin resistant infection were similar to those with colistin susceptible with respect to age, sex, APACHE II score, Charlson comorbidity index, Pitt bacteremia score, prior surgery and the occurrence of polymicrobial cultures. However, patients in the colistin resistant group had lower mortality risk compared to the colistin susceptible (31% vs. 44%, $P = 0.004$ at 14 days; 46% vs. 56% at 28 days, $P = 0.173$; respectively). Multivariable regression analysis confirmed that colistin resistant CR-GNB was associated with significantly lower hazard of inpatient death compared to colistin susceptible infection at 14 days (cause-specific hazard ratio [csHR], 0.53; 95% CI 0.28 - 1.01) and 28 days (csHR, 0.55; 95% CI 0.31 - 0.95) of infection onset.

**Conclusion.** Limited impact of colistin resistance on mortality was demonstrated in a large contemporary cohort of ICU patients with CR-GNB, possibly reflecting the recent shift away from colistin-based treatment regimens.

## INTRODUCTION

Increasing incidence of healthcare-associated infections by carbapenem-resistant (CR) gram-negative bacteria (GNB) has triggered increased use of polymyxins,**[1]** likely fueling the emergence and spread of colistin resistance in CR-GNB clinical isolates.**[2]** The worldwide occurrence of resistance to polymyxins is estimated at less than 10% among GNB, but much higher resistance rates are increasingly being reported in the Mediterranean and South-East Asia regions.**[3]**

Past studies examining clinical outcome of patients colonized or infected with colistin-resistant GNB have produced contradictory findings, ranging from lower to higher mortality rates when colistin resistance is present.**[4–6]** Most studies were carried out before colistin-based treatment regimens were largely replaced by other alternatives and newer antibiotics.**[7–10]** Newer β-lactam antibiotics with or without β-lactamase inhibitors, such as ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam, imipenem/relebactam and cefiderocol, have been largely introduced into clinical practice in the last few years and are now recognized as preferred treatment regimens against CR-Enterobacterales and CR-*P. aeruginosa*. **[9,11]**. For infections by CR-*A. baumannii*, combination regimens, often based on colistin, are the sole therapeutic option when newer options (cefiderocol, sulbactam/durlobactam) are not available. **[12,13]** Nevertheless, it is no longer thought that colistin is the best foundation for treating infections from CR *A. baumannii.* **[11]** In our setting in Greece, based on local susceptibility data and clinical experience, treatment for CR *A. baumannii* is usually based on ampicillin/sulbactam and/or tigecycline. Nonetheless, colistin may still be used in combination with the aforementioned preferred alternatives, or for infections from colistin-susceptible *A. baumannii*. Therefore, reevaluating the effect of colistin resistance on patient outcomes in contemporary cohorts of patients is meaningful and important for optimizing antibiotic stewardship.

The objective of this study was to estimate the excess clinical burden associated with colistin resistance, in terms of the relative risk of inpatient death and the prolongation of hospital stay, in a large contemporary cohort of intensive care unit (ICU) patients with bacteremia from CR GNB.

## METHODS

### Study design

This retrospective cohort study was conducted at the University Hospital of Heraklion, a 750-bed tertiary-care center that serves more than 55,000 inpatients annually and is the referral hospital for the Greek island of Crete. The study cohort included all adult patients ≥ 18 years of age with bacteremia caused by CR-GNB during their stay in the ICU, over a period of 4 years (January 2020 to December 2023). Patients were included once and only their first blood culture positive for CR-GNB was considered. The study size was determined by the number of eligible patients over the study period and no a priori statistical calculation of sample size was performed.

### Outcome endpoints

The primary outcome was all-cause inpatient death in 28 days after the onset of bacteremia (defined as the date of the diagnostic blood culture). Time was restricted up to 28 days of onset of bacteremia in the primary analysis to reduce the likelihood of time varying confounding and outcome misclassification (i.e. death unrelated to the infection). Early and delayed fatalities were examined in secondary analyses of 14-day and overall in-hospital mortality.

### Clinical data

For each patient, we collected data on known prognostic factors and indices, including age, sex, Charlson Comorbidity Index (CCI) upon hospital admission, APACHE II score within 24 hours of admission to ICU, Pitt bacteremia score (PBS) on the day of bacteremia onset, length of hospital stay (LOS) before bacteremia onset, and prior surgery. We also recorded the microorganism(s) isolated and the antibiotic susceptibility test results to account for expected differential prognosis depending on pathogen species [14], the occurrence of polymicrobial infection[15] and the presence of colistin resistance (the latter being the primary exposure of interest). The data were retrieved from electronic patient records and the ICU's information system "CritIS Synergy+" (https://www.critis.gr/critis.html) that automatically captures data from medical devices and from input from ICU staff, in real time, via touch screen monitors at the bedside.

**Microbiology**

Microbial species identification and antimicrobial susceptibility testing were performed with the VITEK 2 automated system, except for colistin susceptibility which was assessed by the broth microdilution method. Carbapenem resistance was defined as a meropenem minimum inhibitory concentration (MIC)>8 mg/L, whereas colistin resistance was defined based on EUCAST breakpoints (MIC>2mg/L for Enterobacterales and *A. baumannii*, MIC>4mg/L for *P. aeruginosa*). Polymicrobial bacteremia was defined as growth of two or more microorganisms in the blood culture. Polymicrobial bacteremia with concurrent colistin-sensitive and colistin-resistant isolates was classified as colistin-resistant.

**Statistical analysis**

To describe mortality risks over time and compare between colistin susceptible and colistin resistant cases, we used cumulative incidence function (CIF) plots estimated by competing risks survival analysis (Aalen-Johansen method), with hospital discharge alive considered as a

competing event to inpatient death.[16–18] CIFs were compared between groups using a modified logrank test.[19]

Cause-specific hazard ratios (csHR) and their 95% confidence intervals were estimated with the Cox proportional hazards model to describe the direct impact of colistin resistance on each competing event of interest (i.e. discharge alive and inpatient death), accounting for variability in baseline covariates. Of note, a low csHR for discharge alive reflects a low daily rate of discharge that results in a prolonged length of hospital stay (LOS). In the Cox models, we adjusted for confounding effects by age, sex, CCI, APACHE II score, LOS, PBS, surgical procedure, polymicrobial bacteremia and pathogen species (*A. baumannii* vs. other). All covariates were measured at baseline, prior to or at bacteremia onset. Multicollinearity was ruled out by examining variance inflation factors (Supplementary Table I). Log-linearity of csHRs for continuous covariates, as assumed by the Cox model, was examined using plots of Martingale residuals (Supplementary Figures 1 and 2). Restricted cubic splines were employed to flexibly model non-linear log hazards for age, CCI and APACHE II score. Proportional hazards in relation to colistin resistance (i.e. a constant effect over time) was confirmed by plots of scaled Schoenfeld residuals and by performing the Grambsch-Therneau test in the multivariable models.

Time zero was set at the time of bacteremia onset for all survival analyses. For the 14-day and 28-day outcomes, event-free time was administratively censored at 14 and 28 days, respectively, when patients remained hospitalized for longer periods. No missing data were observed for any of the study variables. Two-sided *P* values were reported in all analyses and statistical significance was considered at $P < 0.05$. Estimation and modelling of cause-specific CIFs was performed with standard routines for survival analysis in Stata (version 18) after restructuring the data and calculating appropriate weights with the 'stcrprep' user-written command.[19]

**Ethics and reporting**

The study was approved by the hospital's ethics review board (approval no. 08/24-03-2021) and is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[20]

## RESULTS

**Baseline characteristics**

Of 177 unique ICU patients with CR-GNB bacteremia identified over the study period, 134 (76%) had colistin-resistant isolates. *A. baumannii* was the most common pathogen (139 of 177 CR-GNB), which explains the very high proportion of colistin resistance among CR-GNB (87% of CR *A. baumannii* were resistant to colistin). Table I compares baseline characteristics and outcomes between patients with colistin susceptible infection and those with colistin resistant infection. The two groups were fairly similar in their distributions of age, sex, APACHE II score, CCI, PBS, prior surgery and the occurrence of polymicrobial cultures, though patients with colistin-susceptible infection had longer time from admission to onset of bacteremia. Moreover, the distributions of isolated microorganisms were significantly different between the groups, with *A. baumannii* being much more common in the colistin resistant group (Table II).

**Outcomes**

Overall in-hospital mortality was high and 128/177 patients (72%) died in the hospital. Patients with colistin resistant bacteremia appeared to have higher in-hospital mortality compared to those with colistin susceptible bacteremia, but the difference was not statistically significant (75% vs. 65%, respectively; $P = 0.225$). However, patients with colistin resistant infections experienced much longer LOS prior to bacteremia onset compared to those in the colistin

susceptible group (median 24 days vs. 13 days, respectively; *P* = 0.015). When outcomes at 14 and 28 days were examined, the colistin resistant group had lower mortality rates compared to the susceptible group (31% vs. 44%, *P* = 0.004 at 14 days; 46% vs. 56% at 28 days, *P* = 0.173; respectively).

Univariate CIF plots (Figure 1), which account for competing risks and LOS censoring, showed that the daily risk of inpatient death was consistently lower in the colistin resistant group after the first 3-4 days of bacteremia onset and up to 28 days later, but the statistical significance test indicated a high degree of uncertainty (*P* = 0.195). In addition, the colistin resistant group had consistently lower daily probabilities of hospital discharge alive after about the first week of bacteremia onset, which is consistent with longer LOS duration, albeit again not statistically significant (*P* = 0.232). The respective CIF plots for the entire length of hospitalization indicated a possibility of non-proportional death hazards, with colistin resistance accompanied by higher rates for late fatalities (Supplementary Figure 3); however, this analysis was univariate.

Multivariable competing risks regression analysis of 28-day outcomes (Table III), which accounts for variance in the baseline characteristics of patients, confirmed that colistin resistant CR-GNB bacteremia was associated with significantly lower hazard of inpatient death compared to colistin susceptible infection (csHR, 0.55; 95% CI 0.31 - 0.95). The daily rate of discharge alive was also lower in the colistin resistant group, implying prolongation of LOS, albeit the difference from the colistin susceptible group was not statistically significant (csHR, 0.65; 95% CI 0.24 - 1.74).

Results were compatible with lower death hazard in colistin-resistant vs colistin-susceptible CR-GNB bacteremia when we restricted the multivariable analysis to early deaths (14-day mortality csHR, 0.53; 95% CI 0.28 - 1.01) and when we extended the analysis to account for all hospital deaths (in-hospital mortality csHR, 0.74; 95% CI 0.44 - 1.23), notwithstanding a high degree of uncertainty for the latter (Supplementary Table II). Graphical

and test-based assessments of proportional hazards confirmed a time-invariant effect of colistin resistance on patient outcome following adjustment for baseline covariates (Supplementary Figure 4).

Other factors independently and significantly associated with higher hazards of inpatient mortality were CCI and PBS. In contrast, male sex and prior surgery were associated with significantly lower death hazard. Age was independently associated with a lower daily discharge rate leading to LOS prolongation (Supplementary Table III). No baseline covariate appeared to modify the effect of colistin resistance on the hazard of inpatient death as no relevant two-way interaction was statistically significant.

## DISCUSSION

In this large cohort of ICU patients with bacteremia from CR-GNB (predominantly *A. baumannii)* we found that colistin resistance, defined by broth microdilution, was associated with lower 14-day and 28-day in-hospital mortality, independently of several key prognostic indices of patients' underlying condition prior to and at the onset of the infection.

Contrary to our findings, other investigations have reported increased risk of mortality associated with colistin resistance in bacteremias caused by CR-Enterobacterales, predominantly CR-*K. pneumoniae*, [4,10,21,22] and CR-*A. baumannii*. [5,23–25] Two other studies of ICU patients infected by *A. baumannii* in Greece reported lack of statistically significant associations between colistin resistance and mortality. [5,26] However, previous investigations were conducted at a time when colistin-based regimens represented the main treatment option for CR-GNB infection and may have been limited by much smaller numbers of patients compared to our cohort. In contrast, and similar to our findings, an exploratory subgroup analysis of the AIDA trial (comparing colistin monotherapy to colistin/meropenem combination therapy) showed lower mortality in patients with colistin-resistant CR-*A. baumanii* infections.[6] The latter is the only previous study we could find in the literature

reporting findings in full agreement to the present study by showing lower 14-day and 28-day mortality in the presence of colistin resistance.

The reason for lower mortality in infections by colistin-resistant GNB is unclear, but could reflect fitness cost associated with colistin-resistance. [6,27] Colistin resistance (vs. colistin susceptibility) may have an impact on patient outcomes through multiple hypothetical causal pathways that need to be considered when evaluating the clinical burden of colistin resistance. Firstly, inappropriate empirical therapy may be more likely in infections by colistin-resistant pathogens, which in turn may negatively affect outcomes. Furthermore, colistin-based regimens may represent a last resort option for some CR-GNB, especially *A. baumannii*, and colistin-resistance could, in theory, result in worse outcomes due to lack of availability of effective alternative treatment options. On the contrary, colistin resistance may sometimes be associated with fitness cost [27], hence resulting in a less serious infection and potentially better outcomes. Another factor to consider in cohorts that include various pathogenic GNB isolates is potential differences in virulence, and infection severity and outcomes, between different pathogens. Additionally, colistin resistance may be a marker of underlying disease severity, rather than having a direct casual impact on outcomes.

The impact of colistin resistance on fitness cost has not been directly assessed in this study, but was partly accounted for by adjusting for baseline infection severity as measured by PBS. Baseline PBS may also partly account for differences in virulence between the various pathogens. Furthermore, the potential correlation between colistin resistance and underlying disease severity was accounted for in our analyses by adjusting for age, pre-infection length of stay, baseline CCI and APACHE II score. Finally, the impact of availability of treatment options against colistin resistant pathogens was partly accounted for in this study by adjusting for the causal pathogen (*A. baumanii* vs. other). Colistin resistance in *A. baumanii* usually results in pandrug resistance in our setting, [28] which is associated with considerable excess mortality.[14] The optimal treatment for pandrug-resistant *A. baumannii* is not well defined,

257 especially in areas where newer options, such as cefiderocol and sulbactam/durlobactam, are
258 not yet available, but is typically based on various synergistic combination regimens which
259 often include colistin. [9,12,13] On the contrary, there are still good non-polymixin treatment
260 options for CR-Enterobacterales (including ceftazidime/avibactam,
261 meropenem/varbobactam, imipenem/relebactam and the combination of
262 ceftazidime/avibactam with aztreonam). [9,11]

263 In univariate analysis, we noted a possibility for a discordance between short-term
264 (14-day and 28-day) and in-hospital mortality when comparing between the colistin-resistant
265 and colistin-susceptible groups. However, the possibility for a time-variant effect (non-
266 proportional hazards) was eliminated in multivariable analysis when the effects of baseline
267 covariates were accounted for. This was confirmed by thorough graphical and test-based
268 statistical assessments. Moreover, we are confident that short-term mortality reflects more
269 accurately the mortality that is directly attributable to the infection, whereas other factors
270 become more important for patients who remain hospitalized for longer periods (such as
271 underlying comorbidities and their severities).

272 A strength of our study is that it represents a contemporary cohort in a period when
273 newer, non-colistin-based regimens were available. Another strength comes from focusing in
274 ICU patients and the two study groups being similar in terms of most baseline characteristics.
275 Moreover, we included only patients with bacteremia, which are most likely true infections
276 and bypasses the difficulties in differentiating pathogens vs colonizers in other sites of
277 infections. Finally, by adjusting for underlying comorbidity and infection severity, the observed
278 differences in patient outcomes should largely reflect the impact of empirical and definite
279 antibiotic regimens that were used for the treatment of infections by colistin-resistant vs.
280 colistin-susceptible CR-GNB. Therefore, the lower mortality seen in the presence of colistin
281 resistance in this study, likely reflects the availability of alternative treatment options for
282 colistin-resistant CR-GNB infection.

Our study has some limitations, the most important being the retrospective study design and small study size. Although we adjusted for various baseline variables there is still potential for unmeasured confounders. We did not account for the impact of empirical or definite antimicrobial treatment, as assessing treatment success or failure related to therapeutic decisions for specific antimicrobial regimens was beyond our scope in this study; rather, our goal was to evaluate real-life burden of colistin-resistance under usual-care treatment choices. Furthermore, due to the retrospective study design we could not reliably assess the primary site of infection. Moreover, although unlikely for Gram-negative pathogens, it is theoretically possible that a single positive blood culture could represent contamination rather than true infection in few cases [29]. Additionally, the single-center study design means that our result may not be generalizable to other settings. Finally, our study was underpowered and does not rule out the potential impact of colistin resistance on outcomes in specific subgroups of patients.

In conclusion, the findings of this study demonstrate limited impact of colistin resistance on mortality in a large contemporary cohort of intensive care patients with carbapenem-resistant gram-negative bacteremia. This may reflect the recent shift away from colistin-based regimens and towards other preferred alternatives for the treatment of CR-GNB infections.

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## TABLES

**Table I.** Baseline characteristics and outcomes of N = 177 patients with carbapenem-resistant gram-negative bacteremia by colistin resistance status

| Characteristic | Colistin Susceptible (N = 43) | Colistin Resistant (N = 134) | *P* value |
|---|---|---|---|
| Age in years | 69 [58 - 78] | 72 [61 - 79] | 0.503 |
| Male sex | 26 (60%) | 82 (61%) | 0.932 |
| Year of bacteremia onset | | | |
| 2020 | 10 (23%) | 29 (22%) | 0.376 |
| 2021 | 15 (35%) | 44 (33%) | |
| 2022 | 8 (19%) | 41 (31%) | |
| 2023 | 10 (23%) | 20 (15%) | |
| Polymicrobial infection | 7 (16%) | 28 (21%) | 0.508 |
| APACHE II score | 15 [11 - 21] | 14 [10 - 20] | 0.573 |
| Charlson comorbidity index | 4 [2 - 7] | 4 [3 - 6] | >0.999 |
| Pitt bacteremia score | 4 [4 - 6] | 4 [4 - 5] | >0.999 |
| Prior surgery | 14 (33%) | 33 (25%) | 0.306 |
| Pre-infection LOS in days | 24 [9 - 31] | 18 [11 - 29] | 0.075 |
| Post-infection LOS in days | 13 [5 - 32] | 24 [10 - 42] | 0.015 |
| 14-day outcome | | | |
| Remain hospitalized | 19 (44%) | 90 (67%) | 0.004 |
| Died in hospital | 19 (44%) | 41 (31%) | |
| Discharged alive | 5 (12%) | 3 (2%) | |
| 28-day outcome | | | |
| Remain hospitalized | 11 (26%) | 55 (41%) | 0.173 |
| Died in hospital | 24 (56%) | 62 (46%) | |
| Discharged alive | 8 (19%) | 17 (13%) | |
| Hospitalization outcome | | | |
| Discharged alive | 15 (35%) | 34 (25%) | 0.225 |
| Died in hospital | 28 (65%) | 100 (75%) | |

Data are median [interquartile range] or frequency (column percent %). *P* values were calculated using Pearson's chi-squared test for differences in proportions and quantile regression for differences in medians.

Abbreviations: LOS, length of hospital stay

401 **Table II.** Pathogens detected in blood culture of N = 177 patients with carbapenem-
402 resistant gram-negative bacteremia by colistin resistance status
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| **Pathogen detected, n (%)** | Colistin resistance | | |
|---|---|---|---|
| | Susceptible (N = 43) | Resistant (N = 134) | *P* value |
| *Acinetobacter baumanii* | 18 (42%) | 121 (90%) | <0.001 |
| *Achromobacter* | 2 (5%) | 1 (1%) | |
| *Acinetobacter ursingii* | 1 (2%) | 0 (0%) | |
| *Enterobacter aerogenes* | 1 (2%) | 0 (0%) | |
| *Escherichia coli* | 2 (5%) | 0 (0%) | |
| *Klebsiella oxytoca* | 2 (5%) | 1 (1%) | |
| *Klebsiella pneumoniae* | 8 (19%) | 8 (6%) | |
| *Pseudomonas aeruginosa* | 7 (16%) | 1 (1%) | |
| *Pseudomonas putida* | 2 (5%) | 0 (0%) | |
| *Sphigomonas paucimobilis* | 0 (0%) | 1 (1%) | |
| *Stenotrephomonas maltophilia* | 0 (0%) | 1 (1%) | |

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**Table III.** Results of multivariable compering risks regression analysis of 28-day hospital outcomes of N = 177 patients with carbapenem-resistant gram-negative bacteremia

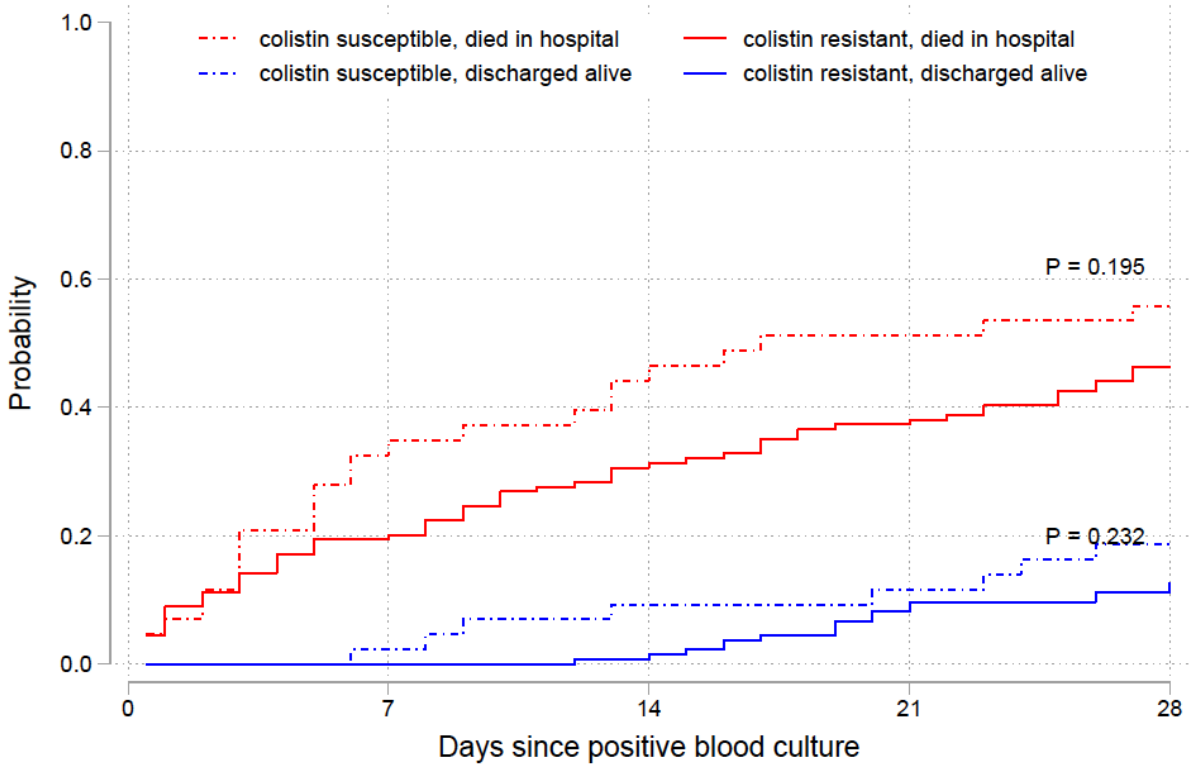
| | Inpatient death | | | | Hospital discharge alive | | |
|---|---|---|---|---|---|---|---|
| **Risk factor** | **csHR** | **95% CI** | | ***P*** | **csHR** | **95% CI** | ***P*** |
| Colistin resistance | 0.55 | 0.31 | 0.95 | 0.032 | 0.65 | 0.24 - 1.74 | 0.386 |
| Age, linear term (per 10 years) | 1.00 | 0.59 | 1.69 | 0.930 | 0.74 | 0.52 - 1.06 | 0.104 |
| Age, spline term | 1.04 | 0.69 | 1.57 | | - | - | - |
| Male sex | 0.59 | 0.38 | 0.91 | 0.018 | 1.87 | 0.72 - 4.83 | 0.197 |
| Prior surgery | 0.70 | 0.40 | 1.23 | 0.218 | 1.02 | 0.42 - 2.48 | 0.967 |
| Polymicrobial culture | 0.56 | 0.30 | 1.06 | 0.075 | 0.71 | 0.26 - 1.95 | 0.502 |
| Pre-infection LOS (per day) | 1.00 | 0.99 | 1.01 | 0.938 | 0.99 | 0.97 - 1.01 | 0.443 |
| Charlson score, linear term (per unit) | 1.57 | 1.00 | 2.46 | 0.004 | 0.81 | 0.60 - 1.10 | 0.185 |
| Charlson score, spline term | 0.75 | 0.48 | 1.18 | | - | - | - |
| APACHE II score, linear term (per unit) | 0.99 | 0.90 | 1.08 | 0.721 | 1.03 | 0.95 - 1.11 | 0.478 |
| APACHE II score, spline term | 1.00 | 0.87 | 1.14 | | - | - | - |
| Pitt bacteremia score (per unit) | 1.17 | 1.04 | 1.33 | 0.012 | 0.85 | 0.67 - 1.06 | 0.153 |
| *A. baumannii* isolated | 1.55 | 0.81 | 2.97 | 0.189 | 0.53 | 0.18 - 1.59 | 0.260 |

**Abbreviations:** csHR, cause-specific hazard ratio; CI, confidence interval; LOS, length of hospital stay.

**Note.** Age, Charlson comorbidity score and APACHE II score were modelled using restricted cubic splines with 3 knots placed at the 5th, 5oth and 95th percentiles. The numeric results for the hazard ratios for covariates modelled with spline terms are not directly interpretable.

415 **FIGURES**

416 **Figure 1**

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## FIGURE LEGENDS

**Figure 1.** Cumulative incidence functions of 28-day inpatient death and hospital discharge alive for N = 177 patients with carbapenem-resistant gram-negative bacteremia in relation to colistin resistance status

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