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Time-Sensitive Antibiotic Adjustments in Gram-Negative Bacteremia: A Survival Perspective

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Background: This retrospective study was designed to assess risk factors for increased 30-day mortality from bacteremia caused by *Escherichia coli* or *Klebsiella pneumoniae* and to calculate the optimal point of time for patients to move from inappropriate empirical antimicrobial therapy to appropriate treatment.

Material/Methods: This retrospective study analyzed data from 610 patients with a diagnosis of *E. coli*- and *K. pneumoniae*-induced bacteremia collected between 2020 and 2023, including population-based information, infection bacteria, comorbidities, and treatment duration. Patients were categorized into 2 groups based on whether they received appropriate empirical antibiotic therapy (AEAT) or inappropriate empirical antibiotic therapy (IEAT). Propensity score-matched (PSM) analysis was performed using 1: 1 nearest neighbor matching. Receiver operating characteristic (ROC) curve analysis determined the time point for patients in the IEAT group to transition to appropriate therapy.

Results: The study found that 30-day mortality was higher in the IEAT group than in the AEAT group (P=0.043). Multifactorial Cox regression analysis after PSM indicated that Pitt score (P<0.001), age-adjusted Charlson comorbidity index score (P<0.001), and inappropriate treatment days (P=0.018) were independent risk factors for increased 30-day mortality. The area under the ROC curve value was 0.613, and the maximum Youden index corresponded to a time turning point of 8 days.

Conclusions: Pitt and aCCI scores and inappropriate treatment days are significant risk factors for increased 30-day mortality in patients with *E. coli* or *K. pneumoniae*. Timely transition from inappropriate antibiotic to appropriate antibiotic therapy within 8 days was found to improve survival.

Keywords: Bacteremia • *Klebsiella pneumonia* • *Escherichia coli*

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Introduction

Bacteremia is a medical condition in which pathogenic bacteria invade the bloodstream, spread along hemodynamic routes, grow profusely in the circulatory milieu, and cause systemic infectious illnesses [1]. Bacteremia could be categorized into 3 types depending on how long the pathogen remains in the blood: transient, intermittent, and persistent [2]. In addition, bacteremia can be categorized into gram-positive and gram-negative bacteremia based on the etiology of the causative organism. *Enterobacteriaceae* bacteria have been reported to account for 88.7% of bacteremia caused by gram-negative bacteria, and *Escherichia coli* and *Klebsiella pneumoniae* are the most common causative organisms among *Enterobacteriaceae* [3]. The incidence of bacteremia caused by multidrug-resistant *E. coli* and *K. pneumoniae* has been increasing yearly [4,5] and has imposed a heavy economic burden on the global public health [6,7]. Especially in developing countries, such as China, the incidence of these infections and their associated socioeconomic effects are more prominent due to limited sanitation and inadequate regulation of antibiotic use.

Notably, *E. coli* and *K. pneumoniae*, the 2 most common species of *Enterobacteriaceae*, are normal flora in the human body [8]. They could invade the human body via multiple pathways, causing similar clinical symptoms, such as fever, chills, and high blood pressure. According to research, *Enterobacteriaceae* account for 88.7% of gram-negative bloodstream infections, with *E. coli* and *K. pneumoniae* as the most common pathogens [3]. The inappropriate use of antibiotics in recent years has exacerbated the evolution of drug-resistant strains, posing a major challenge to clinical management. Notably, *E. coli* and *K. pneumoniae* exhibit similar antibiotic resistance trends, such as bacteria that hydrolyze β-lactam rings primarily by producing extended spectrum β-lactamases (ESBLs) or carbapenemases, thus inactivating the drug, and can be resistant to antibiotics through efflux pump systems [9-11], especially the emergence of multidrug-resistant organisms (MDR), which have made antibiotics, such as cephalosporins, penicillin, and aminoglycosides, increasingly less susceptible. Moreover, it was noted that mortality rates were significantly higher for bacteremia in carbapenem non-susceptible *Enterobacteriaceae* than in sensitive bacteria [12]. Therefore, for patients with *E. coli*- and *K. pneumoniae*-induced bacteremia, early and accurate identification of resistance patterns, as well as timely and effective antibiotic treatments, are particularly important, not only for enhancing patient outcomes but also for lowering the mortality rates [13,14].

The choice of initial empirical antibiotic therapy is critical in clinical practice, as it has been noted that timely and effective empirical antibiotic therapy reduces mortality and length of hospitalization in patients with bacterial infections [15,16], and that inappropriate empirical antibiotic therapy may lead to therapeutic failure, further dissemination of resistant strains, and even an increased risk of death [17]. Studies have shown that for nosocomial bacteremia caused by ESBL-producing *K. pneumoniae* or *E. coli*, inappropriate initial antibiotic treatment is associated with significantly higher mortality than initial treatment with drugs active against these ESBL-producing bacteria [18]. This has led to current research focusing on initial antibiotic selection [19]; however, there is limited research on time-dependent variables associated with empirical antibiotic therapy, such as the effect of different treatment modalities and durations on patient prognosis, and whether a timely shift in inappropriate antibiotic therapy at a given time can change patient prognosis. In addition, the selection and timing of administration of empiric antibiotics varies widely across healthcare organizations, which has led to inconsistencies and controversies in clinical practice [20]. These differences not only affect patient outcomes but also exacerbate the spread of drug-resistant strains and the difficulty of management.

Therefore, this retrospective study aimed to assess the risk factors for 30-day mortality in 610 patients with bacteremia due to *E. coli* and *K. pneumoniae*, and to further calculate the time point for transition to appropriate antibiotics in patients with inappropriate empirical antibiotics therapy, with the aim of providing clinicians with more precise treatment recommendations, which will ultimately improve the prognosis of the patients and reduce the transmission of drug-resistant strains of bacteria.

Material and Methods

Ethical Approval

The study was approved by the Biomedical Research Ethics Committee of the Second Affiliated Hospital of Nanchang University. All methods were performed in accordance with the Declaration of Helsinki guidelines. Given the retrospective design of the study and the use of patients' medical record data, we applied for and obtained an informed consent waiver. To protect patient privacy, anonymization was strictly adhered to throughout the study. All personal information was removed, and each participant was identified by a unique code to ensure data confidentiality during the data processing and analysis phases.

Study Design and Setting

This single-center retrospective cohort study was conducted from January 1, 2020, to December 31, 2023, at the Second Affiliated Hospital of Nanchang University, a tertiary care hospital with more than 2000 beds, located in southeastern China.

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During this period, adult patients (age ≥18 years) with blood culture results of *E. coli* or *K. pneumoniae* who were treated with antibiotics for ≥2 days were enrolled in this study by integrating the laboratory information system and hospital information system databases of this hospital. Exclusion criteria were as follows (1) multiple-organism bacteremia; (2) early death (death within 48 h of bacteremia); (3) outpatients; and (4) cases with missing key data. Analyses were performed only on the first episode of bacteremia for each patient, to ensure homogeneity and clarity of clinical assessment.

According to the Guidelines for the Clinical Use of Antimicrobial Drugs, if the empirical antibiotic used covers a culture-confirmed pathogen and is consistent with the results of a drug sensitivity test, it is considered an appropriate empirical antibiotic treatment (AEAT), otherwise it is considered an inappropriate empirical antibiotic treatment (IEAT). In the present study, patients were divided into 2 groups, the AEAT group and IEAT group, and the clinical results between the 2 groups were compared by dual analysis. First, an unmatched case-control study (n=610) was conducted, and the outcomes of the 431 patients who received AEAT were compared with those of the 179 patients who received IEAT. Second, a propensity score-matched (PSM) case-control study was conducted to examine outcomes in 109 matched pairs of patients who received either IEAT or AEAT. The study cases were defined as patients who received IEAT, whereas controls included those who received AEAT. Patients were observed from the first day of antibiotic therapy through to 30 days, with the endpoint being all-cause in-hospital mortality within 30 days.

Definitions and Outcomes

Diagnosis of bacteremia is based on positive blood culture results. A positive blood culture was defined as isolation of either *E. coli* or *K. pneumoniae* from ≥1 blood culture bottle. Notably, multiple positive bottles from the same patient on the same day were considered a single positive blood culture event.

Bacteremia events were considered hospital-acquired if symptoms appeared >2 days after admission or within 2 days after discharge; otherwise, they were classified as community-acquired infections. Antibiotic efficacy was assessed based on the results of in vitro drug sensitivity tests and with reference to the latest folding point criteria of the Clinical and Laboratory Standards Institute, which classifies bacterial responses to antibiotics as sensitive, intermediary, and resistant. Antibiotic therapy was considered to be efficacious if the pathogen demonstrated in vitro sensitivity or intermediate response, otherwise it was considered ineffective. AEAT was defined as the administration of ≥1 dose of an antibiotic proven efficacious in vitro against isolated *E. coli* or *K. pneumoniae* strains, and if ineffective, was defined as IEAT.

The treatment duration for bacteremia was defined as the number of days from initiation of antibiotic treatment (including the time of IEAT from the start) to the discontinuation of appropriate antibiotic treatment. The primary outcome was mortality at 30 days after bacteremia onset. Clinical responses were categorized as cure, improvement, or failure. Cure entailed a resolution of all infection-related symptoms and signs, along with antibiotic therapy discontinuation. On the other hand, improvement was defined as a complete or partial resolution of all infection-related symptoms and signs, necessitating downgraded continuation with another antibiotic. Finally, failure was defined as no improvement or worsening of infection-related symptoms and signs, or all-cause death.

Data Collection and Processing

In this study, all data were collected and reviewed by 2 professionals through the laboratory information system or hospital information system; missing data items were added by going back to the medical records, and if the percentage of missing items was high and could not be added by other means, the case was excluded from the analysis. The information collected included age, sex, case origin, medical history, microbiological details, comorbidities, records of antibiotic treatments administered, and clinical outcomes. The severity of chronic underlying comorbidities was assessed on the day of admission using the age-adjusted Charlson comorbidity index (aCCI). Acute illness severity was evaluated using the Sequential (sepsis-related) Organ Failure Assessment (SOFA) and Pitt bacteremia scores on the day of positive blood culture detection. All data were collected in Excel tables, and the results were evaluated by subsequent statistical analysis.

Microbiological Tests

Species were identified with either the VITEK-2 Compact system or MALDI-TOF MS (both from bioMérieux, France), with *E. coli* ATCC8739 as the quality control strain for MALDI-TOF MS. Antibiotic susceptibility testing was performed using either the VITEK-2 Compact ASTGN16 card (bioMérieux, France) or the Kirby-Bauer disk diffusion method, with *E. coli* ATCC 25922 and *Staphylococcus aureus* ATCC 29213 as control strains for antibiotic susceptibility testing. Minimum inhibitory concentration values were interpreted based on the Clinical and Laboratory Standards Institute guidelines. All instruments were calibrated regularly and the calibration results were recorded; before each experiment, standard quality control strains were used for quality control to ensure the consistency and accuracy of the experimental results. When there was a discrepancy between different testing methods, troubleshooting was used to determine whether it is due to operational error or equipment failure. If no obvious error was found, re-test was done using the same method, and if the results were still inconsistent after repeating the test, other methods were used for verification.

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Statistical Analysis

All statistical analyses and figure generations were performed using R (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria) and MSTATA (https://www.mstata.com/) software. Tests of normality (Shapiro-Wilk test) and chi-square test (Levene test) were performed on continuous variables to verify the assumptions of the parametric tests, and normally and non-normally distributed variables were expressed as mean±standard deviation (SD) and medians (interquartile ranges [IQR]), respectively. Categorical variables were expressed as cumulative frequencies and percentages. Continuous variables were compared using the Mann-Whitney U test or *t* test, as appropriate, while categorical variables were analyzed using the chi-square test or Fisher exact test.

To minimize selection bias in the AEAT and IEAT groups, we performed PSM analyses of all factors under demographics, sex, acquisition, bacteria, bacterial type, underlying disease, and severity of condition using 1: 1 nearest-neighbor matching, which was performed for PSM analysis with caliper values set at 0.02. To ensure covariate balance between matched groups, a standardized mean difference less than 0.1 was used as a criterion for balance. Independent risk factors for 30-day mortality after PSM were identified using univariate vs multivariate Cox regression models. The relevant variables with $P<0.05$ in the univariate analysis were included in the backward stepwise Cox proportional risk regression model, with those with the highest *P* values progressively excluded until the *P* values of all remaining variables were <0.05. Results were expressed as hazard ratios (HR), 95% confidence intervals (CIs), and *P* values. The turning point for the duration of inappropriate antibiotic treatment was determined using receiver operating characteristic (ROC) curves. Trends in 30-day mortality were compared between the 2 groups using the Kaplan-Meier product limit method. All tests were 2-tailed, and differences or results with $P<0.05$ were considered statistically significant.

Results

Basic Characteristics of Clinical Patients

Herein, 1762 patients diagnosed with gram-negative bacteremia were initially screened, of which 610 cases attributed to *E. coli* or *K. pneumoniae* (431 and 179 patients receiving AEAT and IEAT, respectively) were included after applying the inclusion and exclusion criteria (see Materials and Methodology section for details). **Figure 1** illustrates the detailed enrollment process.

The average age of the 610 patients was 62 (52.0-71.0) years, and 52.30% (319/610) of all patients were men.

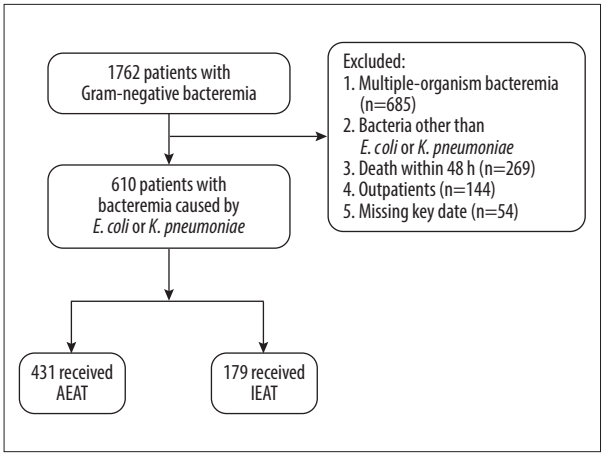

Figure 1. Patient selection flowchart.

Hospital-acquired infections accounted for about 58.03% (354/610) of patients, about 66.89% (408/610) of the patients were infected with bacteremia caused by *E. coli*, and ESBL-positive organisms accounted for 46.07% (281/610) of all cases. Pulmonary infection was the most common underlying comorbidity (36.89%), followed by cardiac disease (36.56%). The 30-day mortality rate was 12.79% (78/610). All patients were categorized into 2 groups based on whether they received appropriate empirical treatment or not: AEAT (n=431) and IEAT (n=179). After calculating the positivity rate of the included variables in each group, we found that the IEAT group had a higher proportion of ICU admissions, intrusive operations, male patients, and hospital-acquired infections. It also had higher rates of ESBL production, carbapenem resistance, and pulmonary infection comorbidities. The 2 groups were well matched for each baseline characteristic after further PSM analyses to reduce the effect of potential bias between them (the specific process of PSM is detailed in the Materials and Methods section). However, the IEAT group had a statistically significantly higher 30-day mortality rate than the AEAT group, with or without PSM analysis (**Table 1**).

Comparison of Drug Susceptibility Information Before and After PSM

Data from the AEAT and IEAT groups before and after PSM were compiled to compare the susceptibility rates of *E. coli* and *K. pneumoniae* isolated against each antimicrobial drug in the 2 patient groups (**Table 2**). Before PSM, besides ertapenem and ampicillin-sulbactam, the 2 groups showed notable differences in susceptibility rates for other antibiotics. After PSM, ertapenem remained the most susceptible antibiotic in both groups, whereas amoxicillin clavulanate potassium, ceftriaxone, cefoxitin, cefepime, cefazolin, and piperacillin tazobactam, all of which have a β-lactam ring structure, remained the antibiotics with significant differences between the 2 groups.

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Table 1. Baseline characteristics of the research population before and after propensity score-matched (PSM) analysis.

Characteristics	Total	Before PSM			After PSM		
	(n=610)	AEAT (n=431)	IEAT (n=179)	*P*	AEAT (n=109)	IEAT (n=109)	*P*
Demographics							
Age median (IQR)	62 (52.0, 71.0)	62 (53.0, 71.0)	62 (52.0, 71.0)	0.558	65 (53.0, 74.0)	62 (51.0, 71.0)	0.231
Admitted 90 days ago (n, %)	160 (26.23)	119 (27.61)	41 (22.91)	0.229	24 (17.39)	28 (18.26)	0.525
Admission to ICU (n, %)	137 (22.46)	82 (19.03)	55 (30.73)	0.002	18 (16.15)	18 (16.15)	>0.999
Intrusive operations (n, %)	431 (70.66)	293 (67.98)	138 (77.09)	0.024	74 (67.89)	80 (73.39)	0.372
Gender (n, %)							
Female	291 (47.70)	219 (50.81)	72 (40.22)	0.017	52 (47.71%)	49 (44.95%)	0.684
Male	319 (52.30)	212 (49.19)	107 (59.78)		57 (52.29%)	60 (55.05%)	
Acquisition (n, %)							
Hospital	354 (58.03)	226 (52.44)	128 (71.51)	<0.001	70 (64.22%)	69 (63.30%)	0.888
Community	256 (41.97)	205 (47.56)	51 (28.49)		39 (35.78%)	40 (36.70%)	
Bacteria (n, %)							
Klebsiella pneumoniae	202 (33.11)	133 (30.86)	69 (38.55)	0.066	29 (26.61%)	26 (23.85%)	0.640
Escherichia coli	408 (66.89)	298 (69.14)	110 (61.45)		80 (73.39%)	83 (76.15%)	
Bacterial type (n, %)							
ESBL	281 (46.07)	181 (42.00)	100 (55.87)	0.002	74 (67.89%)	74 (67.89%)	>0.999
CR	54 (8.85)	5 (1.16)	49 (27.37)	<0.001	5 (4.59%)	5 (4.59%)	>0.999
Underlying disease (n, %)							
Urinary tract infections	96 (15.74)	75 (17.40)	21 (11.73)	0.080	15 (13.76%)	10 (9.17%)	0.288
Lung infections	225 (36.89)	139 (32.25)	86 (48.04)	<0.001	45 (41.28%)	38 (34.86%)	0.329
Immune compromise	118 (19.34)	87 (20.19)	31 (17.32)	0.414	14 (12.84%)	17 (15.60%)	0.561
Brain diseases	90 (14.75)	61 (14.15)	29 (16.20)	0.516	12 (11.01%)	12 (11.01%)	>0.999
Diabetes	113 (18.52)	85 (19.72)	28 (15.64)	0.238	22 (20.18%)	17 (15.60%)	0.377
Cardiovascular disease	223 (36.56)	155 (35.96)	68 (37.99)	0.636	40 (36.70%)	35 (32.11%)	0.476

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Table 1 continued. Baseline characteristics of the research population before and after propensity score-matched (PSM) analysis.

Characteristics	Total	Before PSM			After PSM		
	(n=610)	AEAT (n=431)	IEAT (n=179)	*P*	AEAT (n=109)	IEAT (n=109)	*P*
Severity of condition, median (IQR)							
Pitt score	1 (0.0, 3.0)	1 (0.0. 2.0)	1 (0.0, 4.0)	0.032	1 (0.0, 3.0)	1 (0.0, 2.0)	0.481
Sofa score	4 (2.0, 6.0)	4 (2.0, 5.0)	4 (2.0, 8.0)	0.024	3 (2.0, 5.0)	3 (2.0, 5.0)	0.702
aCCI score	4 (2.0, 5.0)	4 (2.0, 5.0)	4 (2.0, 5.0)	0.757	4 (2.0, 6.0)	4 (2.0, 5.0)	0.237
Treatment median (IQR)							
ITD	0 (0.0, 2.0)	0 (0.0, 0.0)	6 (3.0. 11.0)	<0.001	0 (0.0, 0.0)	5 (3.0, 9.0)	<0.001
ATD	8 (4.0, 12.0)	9 (6.0,14.0)	4 (0.0, 8.0)	<0.001	8 (4.0, 14.0)	5 (1.0, 8.0)	<0.001
Outcome							
30-day mortality (n, %)	78 (12.79)	25 (5.80)	53 (29.61)	<0.001	9 (8.26%)	19 (17.43%)	0.043

ESBL – extended-spectrum β-lactamases producing strains; CR – carbapenem-resistant strains; Sofa – Sequential Organ Failure Assessment; aCCI – age-adjusted Charlson Comorbidity Index; ITD – inappropriate treatment days; ATD – appropriate treatment days.

Comparison of Medication Strategies Before and After PSM

Table 3 further describes the differences in empirical antibiotic administration strategies between the 2 groups. There were no differences in antibiotic dosing strategies between the 2 groups, whether PSM was performed or not. Before PSM, a closer examination of specific antibiotic classes revealed a preference for penicillins (198 vs 34, *P*<0.001), fluoroquinolones (90 vs 59, *P*=0.002), and third-generation cephalosporins (131 vs 91, *P*<0.001) in the AEAT group. After PSM, the AEAT group tended to favor penicillins (54 vs 12, *P*<0.001) and carbapenems (24 vs 6, *P*<0.001). Conversely, the IEAT group resorted more frequently to third-generation cephalosporins (31 vs 61, *P*<0.001) and fluoroquinolones (20 vs 35, *P*=0.019).

Cox Regression Analysis Identified Risk Factors for Increased 30-Day Mortality in Patients

After adjusting for multiple confounders, the inverse stepwise Cox proportional risk regression model analysis revealed that Pitt score (HR: 1.42; 95%CI: 1.25-1.62; *P*<0.001), aCCI score (HR: 1.45; 95%CI: 1.20-1.76; *P*<0.001), and inappropriate treatment days (ITD; HR: 1.07; 95%CI 1.01-1.12: *P*=0.018) were independent risk factors for increased 30-day mortality, which implies that for each 1-point increment in the Pitt score and the aCCI score, the 30-day mortality risk of patients increases by 1.42 and 1.45 fold, respectively. In contrast, 30-day mortality was reduced by 16% for each additional day of appropriate treatment (HR: 0.84; 95% CI: 0.75-0.93; *P*<0.001; Table 4).

ROC Curve Determines the Optimal Time to Change the Appropriate Antibiotic

The ROC curve (Figure 2) was used to determine the time turning point for the 109 IEAT group patients, yielding an AUC value of 0.639 (95%CI: 0.500-0.772), which indicated that the model could predict the time turning point for IEAT group patients. The time point corresponding to the maximum Youden index was found to be 8 days. This means that 8 days can be an important reference point for adjusting treatment strategies, and timely adjustment of inappropriate antibiotics to appropriate antibiotic therapy within 8 days can improve patient outcomes to some extent. To further validate the impact of inappropriate length of empiric antibiotic therapy within vs outside of 8 days on patient survival outcomes, the 179 IEAT group patients were dichotomized based on the determined threshold as follows: group A (ITD <8 days) and group B (ITD >8 days). A comparison of the Kaplan-Meier survival curves between groups A and B (Figure 3) revealed a significantly lower 30-day mortality rate for group A patients (*P*=0.003).

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Table 2. Antimicrobial sensitivity between the 2 groups before and after propensity score-matched (PSM) analysis.

Antimicrobial (n, %)	Before PSM				After PSM			
	Case	AEAT	IEAT	*P*	Case	AEAT	IEAT	*P*
Ampicillin/ sulbactam	227 vs 73	36 (15.86)	5 (6. 85)	0.051	59 vs 49	3 (5.08)	1 (2.04)	0.625
Piperacillin/ tazobactam	431 vs 179	407 (94.43)	106 (59.22)	<0.001	109 vs 109	100 (91.74)	83 (76.15)	0.002
Amoxicillin/ clavulanate	430 vs 179	293 (68.14)	46 (25.70)	<0.001	109 vs 109	66 (60.55)	33 (30.28)	<0.001
Cefazolin	359 vs 137	177 (49.30)	9 (6.57)	<0.001	92 vs 78	23 (25.00)	9 (11.54)	0.025
Ceftriaxone	431 vs 179	248 (57.54)	21 (11.73)	<0.001	109 vs 109	33 (30.28)	20 (18.35)	0.040
Cefepime	431 vs 179	372 (86.31)	82 (45.81)	<0.001	109 vs 109	83 (76.15)	63 (57.80)	0.004
Aztreonam	430 vs 179	316 (73.49)	49 (27.37)	<0.001	109 vs 109	62 (56.88)	40 (36.70)	0.003
Cefoxitin	430 vs 179	345 (80.23)	74 (41.34)	<0.001	109 vs 109	80 (73.39)	58 (53.21)	0.002
Imipenem	431 vs 179	423 (98.14)	131 (73.18)	<0.001	109 vs 109	103 (94.50)	104 (95.41)	0.757
Ertapenem	415 vs 124	415 (100.00)	124 (100.00)	>0.999	103 vs 98	103 (100.00)	98 (100.00)	>0.999
Amikacin	431 vs 179	420 (97.45)	158 (88.27)	<0.001	109 vs 109	103 (94.50)	107 (98.17)	0.280
Gentamicin	430 vs 179	294 (68.37)	92 (51.40)	<0.001	109 vs 109	62 (56.88)	56 (51.38)	0.415
Tobramycin	430 vs 179	290 (67.44)	87 (48.60)	<0.001	109 vs 109	63 (57.80)	53 (48.62)	0.175
Levofloxacin	431 vs 179	147 (34.11)	8 (4.47)	<0.001	109 vs 109	24 (22.02)	6 (5.50)	<0.001
Ciprofloxacin	430 vs 179	203 (47.21)	16 (8.94)	<0.001	109 vs 109	34 (31.19)	13 (11.93)	<0.001
Tigecycline	424 vs 174	416 (98.11)	147 (84.48)	<0.001	108 vs 104	105 (97.22)	101 (97.12)	>0.999
Compound sulfamethoxazole	431 vs 178	250 (58.00)	64 (35.96)	<0.001	109 vs 109	57 (52.29)	39 (35.78)	0.014
Macrodantin (urine)	430 vs 179	307 (71.40)	96 (53.63)	<0.001	109 vs 109	73 (66.97)	74 (67.89)	0.885

Discussion

Increasing research evidence has underscored the high morbidity and mortality rates associated with gram-negative bacteremia [21,22]. Consequently, the present study was a retrospective analysis of 610 patients with bacteremia caused by *E. coli* or *K. pneumoniae*. The results indicated that the Pitt score, aCCI score, and ITD were independent risk factors for an increase in 30-day mortality, while days of appropriate treatment was a protective factor for the increase in 30-day mortality. Furthermore, timely switching from IEAT to appropriate therapy within 8 days could improve the survival outcomes of the patients.

Clinically, the effect of antibiotics (especially penicillins, cephalosporins, and fluoroquinolones) is not always as effective as when they were first used. This phenomenon could be reviewed from the following perspectives. First, the overuse of

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Table 3. Empirical antibiotic treatment between the 2 groups before and after propensity score-matched (PSM) analysis.

Treatment parameter	Before PSM			After PSM		
	AEAT (n=457)	IEAT (n=179)	*P*	AEAT (n=109)	IEAT (n=109)	*P*
Antibiotic treatment strategy [n (%)]						
Monotherapy	309 (71.69)	124 (69.27)	0.549	83 (76.15)	91 (83.49)	0.177
Combination therapy	122 (28.31)	55 (30.73)		26 (23.85)	18 (16.51)	
Antibiotic drug use [n (%)]						
Aminoglycosides	3 (0.70)	1 (0.56)	>0.999	0 (0)	0 (0)	–
Penicillins	198 (45.94)	34 (18.99)	<0.001	54 (49.54)	12 (11.01)	<0.001
Carbapenems	113 (26.22)	36 (20.11)	0.110	24 (22.02)	6 (5.50)	<0.001
Fluoroquinolones	90 (20.88)	59 (32.96)	0.002	20 (18.35)	35 (32.11)	0.019
Tetracyclines	1 (0.23)	0 (0)	>0.999	0 (0)	0 (0)	–
First-generation cephalosporins	1 (0.23)	2 (1.12)	0.207	1 (0.92)	2 (1.83)	>0.999
Second-generation cephalosporins	22 (5.10)	13 (7.26)	0.297	5 (4.59)	6 (5.50)	0.757
Third-generation cephalosporins	131 (30.39)	91 (50.84)	<0.001	31 (28.44)	61 (55.96)	<0.001
Fourth-generation cephalosporins	2 (0.46)	1 (0.56)	>0.999	1 (0.92)	1 (0.92)	>0.999

Table 4. Univariate and multivariate Cox regression analysis of 30-day mortality after propensity score-matched (PSM) analysis.

Characteristic	Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
Pitt score	1.31	1.19-1.44	<0.001	1.42	1.25-1.62	<0.001
aCCI score	1.22	1.04-1.42	0.014	1.45	1.20-1.76	<0.001
Lung infections	2.63	1.23-5.62	0.012	2.00	0.78-5.11	0.149
Immune compromise	0.43	0.10-1.82	0.254	0.18	0.04-0.83	0.028
Diabetes	0.75	0.26-2.15	0.587	0.29	0.09-0.93	0.037
ITD	1.06	1.01-1.10	0.010	1.07	1.01-1.12	0.018
ATD	0.86	0.78-0.95	0.002	0.84	0.75-0.93	<0.001

aCCI – age-adjusted Charlson Comorbidity Index; ITD – inappropriate treatment days; ATD – appropriate treatment days; HR – Hazard Ratio; CI – confidence interval.

clinical antibiotics, untimely adjustment of drug regimens, or incomplete dosages could promote the generation of ESBL-producing bacteria [23]. Second, drug-resistant bacteria could transfer drug-resistant genes through plasmids, accelerating the emergence and dissemination of drug-resistant pathogens [24]. Third, the effectiveness of antibiotic therapy can also be compromised when clinicians are not sufficiently familiar with the bacterial epidemiology of their region. For example, the European Prevalence of Infection in Intensive Care study has noted that antibiotic resistance patterns vary considerably in different regions of Europe [25], and therefore accurate and up-to-date knowledge of local resistance patterns is essential when choosing antibiotics. In this study, the sensitivity of β-lactam ring-containing antibiotics in the IEAT group was generally lower than that of patients in the AEAT group (**Table 2**), which laterally explains the poorer outcome of patients in the

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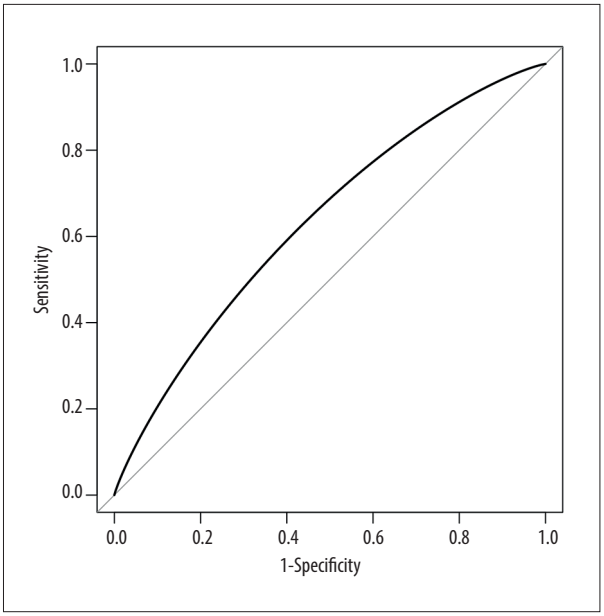

Figure 2. The ROC curve was used to determine the time to transition from inappropriate to appropriate antibiotic treatment for inappropriate empirical antibiotic therapy (IEAT) group patients.

IEAT group with antibiotics such as penicillin and cephalosporin, as well as the association with a higher 30-day mortality rate. This therefore also suggests the need for clinicians to thoroughly consider the epidemiology of *E. coli* and *K. pneumoniae* in the region and to use β-lactam antibiotics cautiously to mitigate outbreaks and epidemics associated with resistant strains that produce ESBLs.

Clinicians often administer empirical antibiotic treatments to patients with bacteremia before receiving blood culture and antibiotic sensitivity results. This phenomenon is always based on the misconception that applying broad-spectrum antibiotics and a combination of multiple antibiotics can effectively suppress the causative microorganisms, thus providing early treatment for patients. However, there is no reliable evidence supporting the use of any antibiotic combination regimen for patients with bacteremia, and some studies have suggested that combination therapy may not necessarily improve the cure rates and reduce the risk of death [26]. In the present study, although therapeutic strategies showed no variance before and after PSM, there were differences in the application of some specific drugs. Therefore, it also reminds clinicians to consider the severity of the patient's condition, likely pathogen type, and history of antimicrobial exposure before prescribing antibiotics, to take into account the antibiotic treatment guidelines in their region [27], and ultimately to make the most appropriate treatment decision for the patient, rather than adopting a combination strategy without any justification.

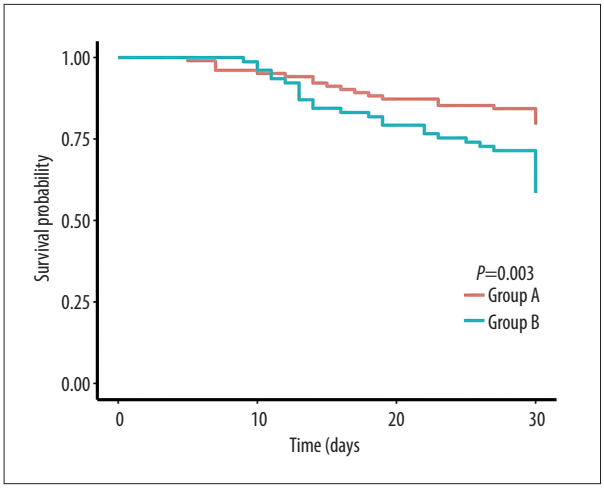

Figure 3. Comparison of 30-day survival curves between patients in groups A and B.

The Pitt score, a simple yet efficacious assessment tool, has been validated for predicting mortality in antibiotic-resistant bacteria-induced and candida species-induced bloodstream infections [28,29]. On the other hand, the aCCI score, which incorporates age and comorbidities, further enhances the prognostic value across a spectrum of diseases for long-term outcomes [30,31]. In this study, the Pitt score and the aCCI score exhibited robust predictive capabilities for the 30-day mortality rate in patients with bacteremia. This observation aligns with findings from other research [32,33], suggesting that these scoring systems demonstrate considerable reliability in prognostic assessment of bacteremia patients. Chen et al proposed the SOFA score as a reliable risk-stratification tool for forecasting 14-day and in-hospital mortality in bacteremia [34]. Conversely, herein, consistent with other reports [35], we did not find SOFA scores to be as prominent. While SOFA scores have been validated for assessing severity and prognosis in patients with sepsis, the present study lacked a notable distinction, which could be attributed to several factors. First, the Pitt score encompasses multiple clinical variables closely associated with severity and prognosis in bacterial infections, such as temperature, heart rate, and respiratory rate, whereas the SOFA score focuses more on organ system functionality indicators. Second, when both scores are applied concurrently, differences in weighting certain criteria or divergent standards for assessing abnormality might arise, influencing their comparative performance.

The choice of initial antibiotics is crucial for patients with bacteremia; however, inappropriate initial therapy still occurs in actual clinical practice. Even after the results of drug sensitivity tests are obtained, the antibiotic regimen may not be adjusted to a more appropriate one in time, for various reasons [36]. Therefore, the duration of empirical antibiotic therapy and the latest time at which a change to an inappropriate antibiotic regimen can be made without affecting the patient's prognosis

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are equally important. Unfortunately, studies on the time-related variables of empirical antibiotic therapy have been underappreciated; therefore, the present study provides some new insights into existing studies by analyzing data on patients with bacteremia due to *E. coli* and *K. pneumoniae* in our region: first of all, for each additional day of ITD, the risk of 30-day mortality in patients increased by a factor of 1.07, whereas for each additional day of appropriate therapy, the risk of death was reduced by 16%. Based on these findings, we have further calculated that 8 days is the critical time point for IEAT to change targeted antibiotics. This finding aligns with numerous previous studies, highlighting the significance of early and appropriate antimicrobial treatment. For instance, Lee et al [37] demonstrated that an inappropriate initial antimicrobial treatment duration was an independent risk factor for a 30-day mortality rate, which concurs with our study results. Falcone et al [38] indicated that the time from blood culture collection to appropriate antibiotic therapy for patients with bloodstream infections caused by KPC-producing *K.* pneumoniae was associated with lower 30-day mortality rates, which supports our conclusion regarding the importance of early adjustment to appropriate antimicrobial treatment. Li et al [39] investigated the influence of IEAT on patients with hospital-acquired pneumonia caused by carbapenem-resistant gram-negative bacteria. Although IEAT did not significantly increase the risk of death within 30 days, the study evaluated carbapenem-resistant gram-negative bacteria-caused hospital-acquired pneumonia in patients, which differed from our study in terms of study subjects and methods. The most prominent advantage of our study compared with other studies is that we calculated the critical time point for converting IEAT to AEAT, providing specific reference information for clinicians and facilitating the optimization of treatment strategies and the improvement of patient survival rates.

Although this study yielded some valuable results, it has to be recognized that the study still has some limitations. First, this study was conducted in a single healthcare organization and was limited to 1 patient group, which limits the generalizability of the findings. Second, although PSM analysis was used in this study to adjust for selection bias factors, there were still unconsidered confounding factors that may have influenced the results. Third, the relatively small sample size was also a shortcoming of this study. Therefore, future studies could expand the sample size for the study in multiple healthcare organizations and include as many factors as possible for the study to improve the external validity of the findings. In addition, drug resistance patterns in different regions should be monitored regularly and treatment guidelines should be updated in a timely manner in order to provide more precise and individualized treatment plans for patients.

Conclusions

This research indicates that the Pitt score, aCCI score, and ITD are significant factors leading to an increased 30-day mortality rate among patients with bacteremia caused by *E. coli* or *K. pneumoniae*. Specifically, for every 1-point increase in the Pitt score and aCCI score, as well as every 1-day increase in ITD, the 30-day mortality risk increased by 1.42 times, 1.45 times, and 1.07 times, respectively. It was also discovered that converting to an appropriate treatment plan within 8 days after the initiation of IEAT can significantly enhance the survival rate of patients.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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