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ORIGINAL RESEARCH

Clinical Characteristics and Prognosis of Hospital-Acquired *Klebsiella pneumoniae* Bacteremic Pneumonia versus *Escherichia coli* Bacteremic Pneumonia: A Retrospective Comparative Study

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Objective: This research aimed to investigate the variations in clinical features and prognosis of HABP caused by *E. coli* and *K. pneumoniae*. We also aimed to evaluate the risk variables related to 30-day death in the investigated groups.

Methods: A single-center retrospective cohort research lasting four years was performed. A total of 117 patients with HABP were involved in this research. The primary prognosis was 30-day death.

Results: Among 117 patients with HABP, 60 patients were infected with *K. pneumoniae* (KP-HABP), and 57 patients were infected with *E. coli* (E. coli-HABP). A higher proportion of males, ICU admission, undergoing tracheotomy and trachea cannulation, carbapenem-resistant strains, inappropriate empirical therapy (IET), immune compromise, diabetes mellitus, and sepsis were observed in the patients with KP-HABP (all $P < 0.05$). Meanwhile, the median SOFA score and Pitt score were significantly ($P < 0.001$) higher in the KP-HABP group compared to the E. coli-HABP group. The 30-day death was 48.33% in the KP-HABP group and 24.56% in the E. coli-HABP group ($P = 0.008$). After adjusting for the main covariates, the hazard ratios for 30-day mortality in KP-HABP were 1.58 (95% CI:0.80–3.12), 3.24 (95% CI:1.48–7.06), 5.67 (95% CI:2.00–16.07), and 5.99 (95% CI:2.10–17.06), respectively. Multivariate logistic regression models revealed that IET, hypoproteinaemia, cerebral vascular disease (CVD), and SOFA score ≥ 5.0 were the independent risk variables for 30-day death in KP-HABP. Simultaneously, SOFA score ≥ 4.0 and Pitt score ≥ 2.0 were independent risk factors for 30-day mortality in E. coli-HABP.

Conclusion: The clinical features of HABP vary depending on whether it is caused by *Escherichia coli* or *K. pneumoniae*. KP-HABP patients have higher 30-day mortality than E. coli-HABP patients. To ensure greater validity, it is necessary to further verify this conclusion using a larger sample size.

Keywords: *Escherichia coli*, *Klebsiella pneumoniae*, hospital-acquired pneumonia, bacteremic pneumonia, 30-day mortality

Introduction

The high incidence of hospital-acquired pneumonia (HAP) has a serious impact on the safety and prognosis of patients, which increases the economic burden on society and patients.[1,2] Previous studies reported that the prevalence of HAP is estimated to be 0.5% to 1.0% and accounts for approximately 25% of all infectious diseases in the intensive care unit (ICU).[3] Furthermore,

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hospital-acquired bacteremic pneumonia (HABP) poses a significant public health threat because of the high mortality rate, high cost, and high rate of detection of bacterial resistance.[3–5]

The leading etiological agents in HAP are Gram-negative bacteria. Opportunistic pathogens, which have the ability to colonize either the respiratory or intestinal tracts of humans or animals, have a tendency to infect individuals with compromised immune systems.[6] *Klebsiella pneumoniae* (*K. pneumoniae*) and *Escherichia coli* (*E. coli*), as the two most representative bacteria of the Enterobacteriaceae family, are the two common pathogens of HABP.[7] A large epidemiological study analyzed the pathogenic bacteria in HABP patients (31,436 episodes) and found that Gram-negative bacteria were the most common isolates, with *Klebsiella pneumoniae* (9.8%) and *E. coli* (6.9%) infections being the third and fourth most common, respectively.[8] Notably, recently, due to clinical antibiotic abuse and other reasons, bacterial resistance has become increasingly severe,[9] which has led to the evolution of these two bacteria into produced Extended-spectrum beta-lactamase (ESBL) and carbapenem-resistant (CR) strains, which certainly have great difficulty in the clinical therapy of HABP.[10–12]

In effect, it is critical to identify the causative pathogens as soon as possible for the treatment of HABP. Different bacteria have different pathogenic mechanisms,[13] along with complex risk factors, comorbidities, and inappropriate empirical therapy. This contributes to prolonged hospitalizations and higher healthcare expenses, eventually leading to a worse prognosis for patients with HABP.[8,14,15] Although numerous studies examined the differences in bloodstream infections induced by *E. coli* and *K. pneumoniae*,[16–18] a comprehensive comparison of HABP caused by these two pathogens is still lacking.

This research objectives were to analyze the clinical features and outcome of HABP related to *E. coli* and *K. pneumoniae* and to assess the risk factors for 30-day death in each group separately, with the aim of providing a reference for clinical diagnosis, treatment, and rational use of antibiotics.

Methods

Study Subjects

This retrospective cohort research was conducted over four years (2016–2019). HAP and ventilator-associated pneumonia (VAP) have been identified based on the clinical practice standards of the Infectious Diseases Society of America and the American Thoracic Society.[19] A total of 117 adults patients with HABP caused by *E. coli* or *K. pneumoniae* from the Second Affiliated Hospital of Nanchang University were involved herein (Figure 1). According to the different pathogens, patients with HABP were further classified into hospital-acquired *Klebsiella pneumoniae* (KP) bacteremic pneumonia (KP-HABP) group (n = 60) and hospital-acquired *E. coli* bacteremic pneumonia (E. coli-HABP) group (n = 57). Subsequently, patients with KP-HABP were split into two groups: death (n = 29) and survival (n = 31) based on their 30-day death. Similarly, patients with E. coli-HABP were divided into the survival group (n = 43) and the deceased group (n = 14). The inclusion criteria were: (1) Patients were aged 18 and above; (2) Patients with a minimum of one positive blood culture for *Klebsiella pneumoniae* or *E. coli* within 24 h of the diagnosis of HAP. The exclusion criteria were: (1) Polymicrobial infection; (2) Infections other than pneumonia at the time of admission; (3) Pregnant women and lactating females; (4) Patients with missing clinical data. For patients with multiple *E. coli* or *K. pneumoniae* blood culture isolations, only the initial isolation from each patient was incorporated herein.

Study Definitions and Treatment Outcomes

HAP was defined as pneumonia that does not exist at the time of hospitalization and is not in the incubation period of infection but occurs 48 h after hospitalization, including pneumonia acquired in the hospital and occurring within 48 h of discharge (including VAP).[19] The current diagnosis of pneumonia is based on imaging showing a new pulmonary infiltrate and clinical evidence confirming that the infiltrate is due to infection, including new fever, pus sputum, leukocytosis, and decreased oxygenation.[20] Polymicrobial infection was defined as more than one microorganism detected by blood culture or respiratory secretion specimens within 48 h of admission. At the time of hospitalization, immunocompromised patients are administered chronic glucocorticoids, biologic response modifiers, antimetabolites, or immunosuppressive transplant medicines.[21] Inappropriate empirical antimicrobial therapy (IET) was defined as the isolates that were insusceptible (the susceptibility test results are interpreted as

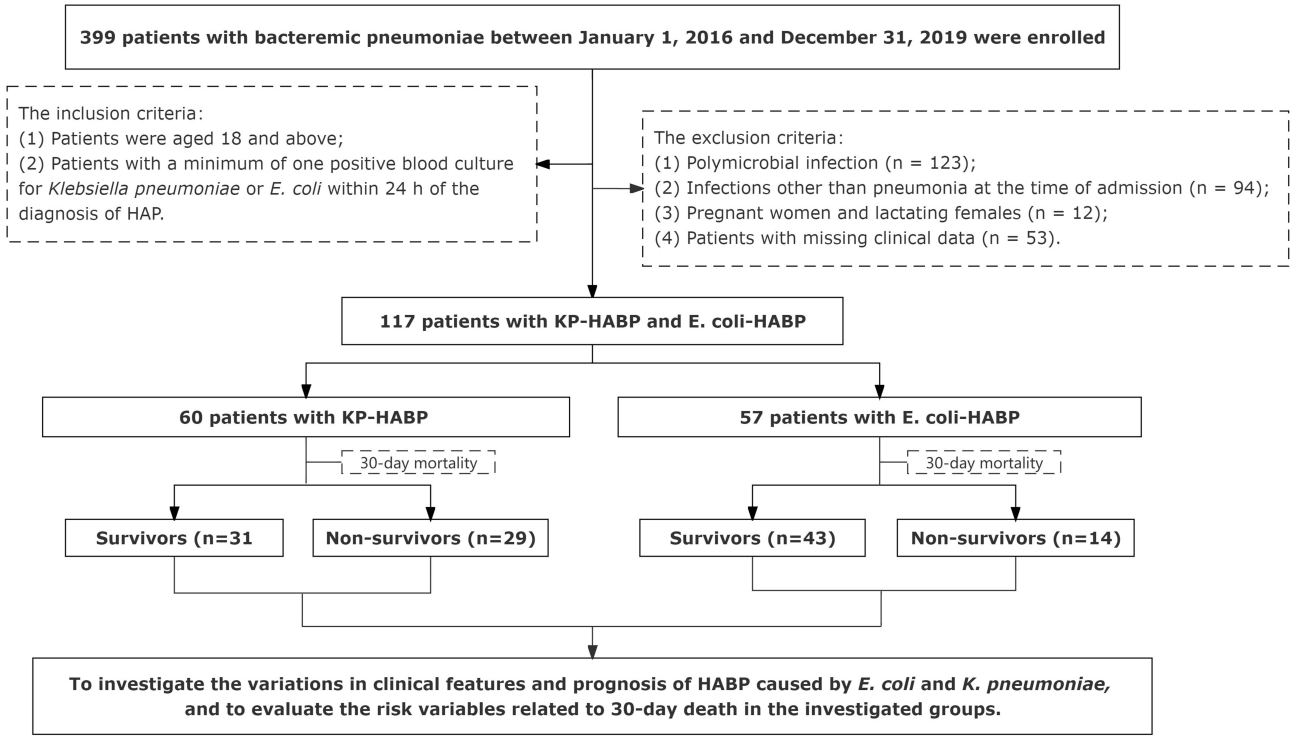

Figure 1 Flow chart of the inclusion of patients with KP-HABP and E. coli-HABP.

"resistant" (R) or "intermediate" (I)) to the prescribed antibiotics. The presence of infection, recurrence, or progression of disease after two weeks of appropriate antibiotic therapy was regarded as a 14-day therapeutic failure. The primary prognosis was 30-day mortality, and the secondary prognosis was 14-day treatment failure.

Data Collection

All patient data was acquired from digital medical data. Microsoft Excel (Excel for MacOS, 2020) was used for data collection of the clinical and laboratory information, including demographics, inpatient department, invasive procedures, underlying disease, microbiology-related data, infection-related indices, and the use of antibiotics, disease severity, and patient outcomes. Comorbidity was assessed using the age-adjusted Charlson comorbidity index (aCCI).[22] Meanwhile, to evaluate the disease severity of patients with HABP, the Pitt bacteremia score (Pitt score)[23] and the Sequential Organ Failure Assessment (SOFA) score[24] were calculated on the day of admission.

Microbiological Analysis

KP and *E. coli* isolates were identified using mass spectrometry (MALDITOF MS, Vitek MS, BioMérieux, France) or the Vitek 2 automated System (BioMerieux®, Marcy IEtolie, France) according to the manufacturer's instruction. Susceptibility tests were performed with the ATB System (bioMérieux, France) or Kirby-Bauer (KB) test. The minimal inhibitory concentration (MIC) was detected by the broth microdilution approach.[25] The combined disc technique (ceftriaxone only and ceftriaxone-clavulanic acid) was used to detect ESBL production. Carbapenemase production was tested using the modified carbapenem inactivation method (mCIM) and the EDTA-modified carbapenem inactivation method (eCIM). Clinical Laboratory Standards Institutes (CLSI) standards (CLSI, 2016–2019) were used to interpret all susceptibility data.[26–29]

Statistics

SPSS v22.0 was employed to analyze the data (SPSS Inc.). GraphPad Prism 7.0 (GraphPad Software Inc.) and R software (R project) were employed to plot all figures. For data (in line with normal distribution) that was presented as mean ± standard deviation, a parameter test was used (One-way analysis of variance). The non-parametric *Mann–*

Whitney U-test was performed for data that did not follow a normal distribution and was provided as a median and IQR. Percentages were calculated using the chi-square or Fisher's exact test on the numerical data. Kaplan-Meier (KM) curve was plotted to assess survival outcomes between KP-HABP and E. coli-HABP. Following this, to assess the hazard ratios (HR) and 95% confidence interval (CI) of the correlation of HABP due to two pathogens with poor outcomes (14-day treatment failure and 30-day mortality), four Cox regression adjusted models were constructed. Model 1 was adjusted for age, sex, inpatient department (surgery ward, ICU), and invasive procedures (tracheotomy, trachea cannula). Model 2 was further adjusted for bacterial type. Model 3 was further adjusted for underlying disease (immune compromise, diabetes mellitus, and sepsis), Pitt score, and SOFA score. Model 4 was further adjusted for IET. Subsequently, the optima cut-off values of SOFA score, Pitt score, and aCCI score were calculated by receiver operating characteristic (ROC) curves and categorized using the optima cut-off values.

Moreover, univariate and multivariate logistic regression analyses were employed to detect independent risk variables for 14-day treatment failure and 30-day death in patients with KP-HABP and E. coli-HABP, respectively. Then, variables with $P < 0.10$ (with potentially statistically significant) in the multivariate logistic analyses for 30-day mortality were included for nomogram construction. The Hosmer-Lemeshow test was employed to analyze the nomogram's calibration and determine its accuracy.[30] Finally, the nomogram was assessed utilizing the ROC curve, calibration curve, and decision curve analysis (DCA). A *P*-value smaller than 0.05 ($P < 0.05$) was considered statistically significant.

Results

The Initial Demographics and Clinical Features of Subjects with KP-HABP and E. Coli-HABP

Table 1 depicts the clinical features of patients with KP-HABP and E. coli-HABP. In total, 117 patients were diagnosed with KP-HABP or E. coli-HABP, with a mean age of 57.88 ± 16.06 years, and 69 (58.97%) males. A total of 60 patients

Table 1 Characteristics of the KP-HABP and E. Coli-HABP Cohorts

	Total (n=117)	KP-HABP (n=60)	E. Coli-HABP (n=57)	t/Z/x^2	*P* value
Demographics					
Age, years (mean±SD)	57.88±16.06	57.03±17.58	58.77±14.39	−0.587	0.559
Sex (n, %)					
Male	69 (58.97)	42 (70.00)	27 (47.37)	6.188	0.013
Female	48 (41.03)	18 (30.00)	30 (52.63)		
Inpatient department (n, %)					
Internal Medicine	44 (37.61)	22 (36.67)	22 (38.60)	0.046	0.829
Surgery Ward	35 (29.91)	10 (16.67)	25 (43.86)	10.310	0.001
ICU	27 (23.08)	22 (36.67)	5 (8.77)	12.813	<0.001
Invasive procedures (n, %)					
Surgery	35 (29.91)	15 (25.00)	20 (35.09)	1.419	0.234
Venous catheterization	21 (17.95)	12 (20.00)	9 (15.79)	0.352	0.553
Wound drainage tube	10 (8.55)	3 (5.00)	7 (12.28)	1.160	0.281
Indwelling urinary catheter	18 (15.38)	12 (20.00)	6 (10.53)	2.015	0.156
Bone marrow aspiration	18 (15.38)	9 (15.00)	9 (15.79)	0.014	0.906
Lumbar puncture	9 (7.69)	6 (10.00)	3 (5.26)	0.377	0.539
Thoracentesis	5 (4.27)	3 (5.00)	2 (3.50)	0.159	0.690
Tracheotomy	40 (34.19)	30 (50.00)	10 (17.54)	13.685	<0.001
Trachea cannula	33 (28.21)	25 (41.67)	8 (14.04)	11.021	0.001
Bacterial type (n, %)					
ESBL/AmpC-producing strains	40 (34.19)	11 (18.33)	29 (50.88)	13.759	<0.001
Carbapenem-resistant strains	26 (22.22)	25 (41.67)	1 (1.75)	26.941	<0.001
Underlying disease (n, %)					

(*Continued*)

Table 1 (Continued).

	Total (n=117)	KP-HABP (n=60)	E. Coli-HABP (n=57)	t/Z/x^2	*P* value
Immune compromise	35 (29.91)	23 (38.33)	12 (21.05)	4.163	0.041
Cerebral vascular disease	41 (35.04)	25 (41.67)	16 (28.07)	2.374	0.123
Hypertension	42 (35.90)	22 (36.67)	20 (35.08)	0.032	0.859
Diabetes mellitus	15 (12.82)	12 (20.00)	3 (5.26)	5.680	0.017
Pleural effusion	25 (21.37)	12 (20.00)	13 (22.81)	0.137	0.711
Hypoproteinaemia	31 (26.50)	17 (28.33)	14 (24.56)	0.214	0.644
Leukaemia	22 (18.80)	13 (21.67)	9 (15.79)	0.661	0.416
Sepsis	89 (76.07)	56 (93.33)	33 (57.89)	20.166	<0.001
Infection-related indices (median, IQR)					
C-reactive protein (mg/L)	124.56 (74.52, 175.69)	138.63 (75.88, 173.10)	104.00 (67.29, 181.70)	−0.638	0.523
Procalcitonin (ng/mL)	2.51 (0.98, 9.61)	2.70 (0.93, 14.38)	2.45 (1.08, 8.58)	−0.068	0.946
Disease severity (median, IQR)					
Pitt score	2.0 (1.0, 5.0)	3.0 (1.0, 7.0)	1.0 (0.0, 3.0)	−4.112	<0.001
SOFA score	5.0 (3.0, 8.0)	5.0 (4.0, 9.0)	3.0 (2.0, 6.0)	−3.835	<0.001
aCCI score	4.0 (2.0, 5.0)	4.0 (2.0, 6.0)	4.0 (2.0, 5.0)	−0.670	0.503
Empiric therapy (n, %)					
Third-generation cephalosporins	9 (7.69)	4 (6.67)	5 (8.77)	0.006	0.936
BLBLI	40 (34.19)	18 (30.00)	22 (38.60)	0.960	0.327
Carbapenems	49 (41.88)	30 (50.00)	19 (33.33)	3.368	0.068
Aminoglycoside	4 (3.42)	3 (5.00)	1 (1.75)	0.209	0.648
Inappropriate empirical therapy	40 (34.19)	28 (46.67)	12 (21.05)	8.523	0.004
Antibiotics ≥3 during hospitalization (n, %)	40 (34.19)	23 (38.33)	17 (29.82)	0.941	0.332
Outcomes (n, %)					
14-day treatment failure	59 (50.43)	40 (66.67)	19 (33.33)	12.992	<0.001
30-day mortality	43 (36.75)	29 (48.33)	14 (24.56)	7.106	0.008
Length of hospital stay (mean±SD)	25.0 (17.0, 35.0)	28.5 (18.0, 38.0)	24.0 (16.0, 30.0)	−1.315	0.189

Abbreviations: KP, *Klebsiella pneumoniae; E. coli, Escherichia coli*; HABP, Hospital-acquired bacteraemia pneumonia; ICU, intensive care unit; ESBL, extended-spectrum β-lactamase; Pitt score, Pitt bacteremia score; SOFA, sequential organ failure assessment; aCCI, age-adjusted Charlson comorbidity index; BLBLI, β-lactam-β-lactamase inhibitor.

were from the KP-HABP group, and 57 were from the E. coli-HABP group. No statistically significant variation was observed in age, the proportion of patients admitted to internal medicine, invasive procedures (including surgery, venous catheterization, wound drainage tube, indwelling urinary catheter, bone marrow aspiration, lumbar puncture, and thoracentesis), underlying disease (including cerebral vascular disease, hypertension, pleural effusion, hypoproteinaemia, and leukemia), aCCI score, empiric therapy (including third-generation cephalosporins, β-lactam-β-lactamase inhibitor, carbapenems, and aminoglycoside), antibiotics ≥3 during hospitalization and hospitalization duration between the two groups (all $P > 0.05$). Nevertheless, in comparison to the E. coli-HABP group, patients with KP-HABP included more male patients, were more frequently admitted to the ICU, less frequently admitted to the surgery ward, and were more likely to undergo tracheotomy and trachea cannulation. Moreover, the KP-HABP group exhibited a higher proportion of carbapenem-resistant strains and inappropriate empirical therapy, a higher prevalence of concomitant immune compromise, diabetes mellitus, and sepsis, higher Pitt and SOFA scores, and a higher proportion of 14-day therapeutic failure and 30-day mortality (all $P < 0.05$). Table 2 presents the antimicrobial susceptibility features of 60 *K. pneumoniae*, and 57 *E. coli* isolates. Compared to *K. pneumoniae, E. coli* was sensitive to more antibiotics, including amikacin, cefoxitin, imipenem, and piperacillin (all $P < 0.05$).

The Hazard Ratio for 30-Day Mortality According to KP-HABP and E. Coli-HABP

The 30-day mortality was 48.33% (29/60) in the KP-HABP group compared to 24.56% (14/57) in the E. coli-HABP group ($P = 0.008$). Subsequently, Kaplan-Meier survival analysis was performed to assess the relationship between the bacterial

Table 2 Antimicrobial Resistance of *Klebsiella Pneumoniae* and *Escherichia Coli* Isolated from Patients with KP-HABP and E. Coli-HABP

Antimicrobial (n, %)	*Klebsiella pneumoniae* (n=60)			*Escherichia coli* (n=57)			*P* value[a]
	S	I	R	S	I	R	
Amikacin	46 (76.67)	–	14 (23.33)	56 (98.25)	–	1 (1.75)	<0.001
Aztreonam	34 (56.67)	–	26 (43.33)	38 (66.67)	–	19 (33.33)	0.266
Ciprofloxacin	19 (31.67)	3 (5.00)	38 (63.33)	21 (36.84)	5 (8.77)	31 (54.39)	0.555
Gentamicin	39 (65.00)	–	21 (35.00)	33 (57.89)	–	24 (42.11)	0.430
Ceftriaxone	25 (41.67)	–	35 (58.33)	25 (43.86)	–	32 (56.14)	0.811
Cefoxitin	31 (51.67)	1 (1.67)	28 (46.67)	43 (75.44)	4 (7.02)	10 (17.54)	0.008
Cefixime	30 (50.00)	–	30 (50.00)	46 (80.70)	–	11 (19.30)	0.423
Tobramycin	38 (63.33)	5 (8.33)	17 (28.33)	31 (54.39)	19 (33.33)	7 (12.28)	0.325
Imipenem	35 (58.33)	–	25 (41.67)	56 (98.25)	–	1 (1.75)	<0.001
Levofloxacin	19 (31.67)	8 (13.33)	33 (55.00)	11 (19.30)	24 (42.10)	22 (38.60)	0.126
Piperacillin	32 (53.33)	3 (5.00)	25 (41.67)	52 (91.23)	4 (7.02)	1 (1.75)	<0.001

Note: [a]Comparison of antimicrobial susceptibility between two groups.
Abbreviations: KP, *Klebsiella pneumoniae; E. coli, Escherichia coli*; HABP, Hospital-acquired bacteraemia pneumonia; S, susceptible; I, intermediate-resistant; R, resistant.

type of hospital-acquired pneumonia and survival outcomes (Figure 2). Similar to the results above, patients with KP-HABP presented a significant increase in 30-day mortality ($P < 0.001$). Then, to evaluate possible determinants of 30-day mortality from KP-HABP and E. coli-HABP, four multivariate Cox regression models were developed (Table 3). After adjusting for age, sex, inpatient department (surgery ward, ICU), and invasive procedures (tracheotomy, trachea cannula), the HR for 30-day mortality comparing KP-HABP to E. coli-HABP was 1.58 (95% CI [0.80–3.12], $P = 0.187$, model 1). Further analyses adjusted for bacterial type, revealing a statistically significant adjusted HR (HR = 3.24, 95% CI [1.48–7.06], $P = 0.003$, model 2). Moreover, HR remained statistically significant after adjustment for underlying disease (immune compromise, diabetes mellitus, sepsis), Pitt score and SOFA score (HR = 5.67, 95% CI [2.00–16.07], $P = 0.001$, model 3), and after further adjustment for inappropriate empirical therapy (HR = 5.99, 95% CI [2.10–17.06], $P = 0.001$, model 4). However, there was a greater proportion of 14-day treatment failure in the KP-HABP group compared E. coli-HABP group (66.67% vs 33.33%), even though the variation was non-statistically significant after adjusting by models (Table 3).

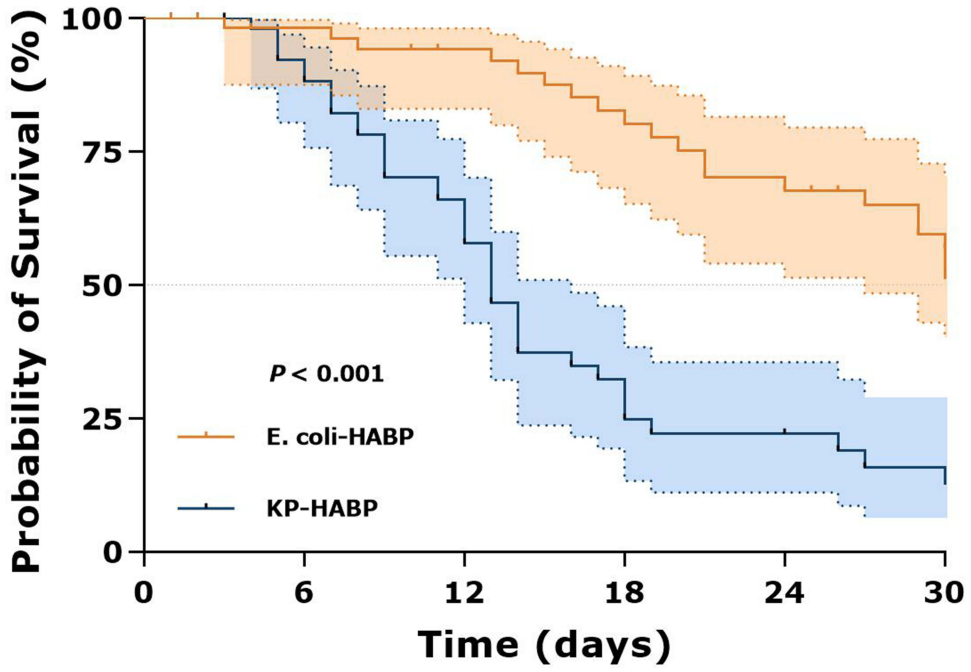

Figure 2 Kaplan-Meier curve of 30-day mortality in patients with HABP caused by *Klebsiella pneumoniae* and *Escherichia coli*.

Table 3 Hazard Ratio for Outcomes According to KP-HABP and E. Coli-HABP

	Events/total n, %	HR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
14-day treatment failure					
KP-HABP	40 (66.67)	1.71 (0.97–3.01)	1.16 (0.47–2.88)	1.32 (0.47–3.68)	1.00 (0.34–2.92)
E. coli-HABP	19 (33.33)	Ref	Ref	Ref	Ref
P value	< 0.001	0.064	0.747	0.602	0.999
30-day mortality					
KP-HABP	29 (48.33)	1.58 (0.80–3.12)	3.24 (1.48–7.06)	5.67 (2.00–16.07)	5.99 (2.10–17.06)
E. coli-HABP	14 (24.56)	Ref	Ref	Ref	Ref
P value	0.008	0.187	0.003	0.001	0.001

Notes: Model 1: Adjusted for age, sex, inpatient department (surgery ward, ICU) and invasive procedures (tracheotomy, trachea cannula). Model 2: Further adjusted for bacterial type. Model 3: Further adjusted for underlying disease (immune compromise, diabetes mellitus, sepsis), Pitt score and SOFA score. Model 4: Further adjusted for inappropriate empirical therapy.
Abbreviations: CI, confidence interval; HR, hazard ratio.

The Risk Variables for 14-Day Treatment Failure and 30-Day Death in Patients with KP-HABP

Patients with KP-HABP were classified into survival (n = 31) or non-survival group (n = 29) based on the prognosis of patients at 30 days. Table 4 shows the different features of the death group and survival group. In comparison to the survival group, the death group showed an increased rate of tracheotomy, was more susceptible to carbapenem-resistant strains infection, and had higher numbers of subjects with cerebral vascular disease and hypoproteinaemia, higher Pitt score, higher SOFA score, and aCCI score. Meanwhile, the death group exhibited a greater proportion of inappropriate empirical therapy, antibiotics ≥3 during hospitalization, and 14-day treatment failure.

Due to Pitt, SOFA, and aCCI scores being non-normal data, the cut-off values of these parameters were calculated with the ROC curve analysis (Table 5). The best cut-off levels of Pitt, SOFA, and aCCI scores were 3.0, 5.0, and 5.0, respectively. After dichotomous transformation, univariable and multivariable logistic regression analyses were carried out to assess the 14-day treatment failure and 30-d mortality-related risk factors in patients with KP-HABP (Figure 3). Subsequently, multivariable logistic regression showed carbapenem-resistant strains, cerebral vascular disease and higher SOFA score (≥ 5.0) were potential predictors of 14-day treatment failure ($P < 0.10$, with potentially statistically significant) (Figure 3B), and inappropriate empirical therapy (IET), hypoproteinaemia, cerebral vascular disease (CVD) and higher SOFA score (≥ 5.0) were related significantly to 30-day deaths in patients with KP-HABP ($P < 0.05$) (Figure 3D).

Furthermore, the nomogram was constructed by incorporating five predictors, which were linked to 30-day death (Figure 4). The scores corresponding to the nomogram were 87.5 for CVD, 90 for hypoproteinaemia, 100 for SOFA score ≥ 5.0, 72.5 for aCCI score ≥ 5.0, and 97.5 for IET, respectively, with predicted probabilities between 0.05–0.99 for total integrals between 65–430. The AUC of the nomogram was 0.888 (95% CI: 0.800–0.977), with 82.8% sensitivity and 87.1% specificity, which had high accuracy (Figure 5A). The calibration curve was approximately diagonal, and the Hosmer-Lemeshow test *P*-value for the model's goodness-of-fit was 0.491, which is not statistically significant (Figure 5B). Finally, the clinical decision curve (DCA) for the 30-day mortality prediction model was presented in Figure 5C, which showed great clinical application value.

The Risk Variables for 14-Day Treatment Failure and 30-Day Mortality in Patients with E. Coli-HABP

The patient cohort diagnosed with E. coli-HABP was divided into two distinct groups based on their survival status at 30 days post-admission: survival (n = 43) and death (n = 14) (Table 4). The percentage of tracheotomy and trachea cannula was higher in the death group than in the survival group. Concerning sepsis severity, patients in the death group showed significantly higher Pitt and SOFA scores. In addition, Patients in the death group were significantly more likely to receive inappropriate empirical therapy and to have treatment failure at the 14-day point. Meanwhile, based on Youden's

Table 4 Characteristics of 30-Day Survivors and Non-Survivors

Variable	KP-HABP (n=60)				E. Coil-HABP (n=57)			
	Survivors (n=31)	Non-Survivors (n=29)	t/Z/x^2	*P* value	Survivors (n=43)	Non-Survivors (n=14)	t/Z/x^2	*P* value
Demographics								
Age, years (mean±SD)	53.26±15.76	61.07±18.77	1.740	0.088	57.95±13.49	61.29±17.18	0.662	0.516
Sex (n, %)								
Male	23 (74.19)	19 (65.52)	0.537	0.464	18 (41.96)	9 (64.29)	2.130	0.144
Female	8 (25.81)	10 (34.48)			25 (58.14)	5 (35.71)		
Inpatient department (n, %)								
Internal Medicine	12 (38.71)	10 (34.48)	0.115	0.734	14 (32.56)	8 (57.14)	2.693	0.101
ICU	8 (25.81)	14 (48.28)	3.258	0.071	3 (6.98)	2 (14.29)	0.087	0.767
Invasive procedures (n, %)								
Surgery	8 (25.81)	7 (24.14)	0.022	0.881	15 (34.88)	5 (35.71)	<0.001	>0.999
Venous catheterization	4 (12.90)	8 (27.59)	2.109	0.155	5 (11.63)	4 (28.57)	1.184	0.277
Wound drainage tube	2 (6.45)	1 (3.45)	<0.001	>0.999	6 (13.95)	1 (7.14)	0.042	0.837
Indwelling urinary catheter	7 (22.58)	5 (17.24)	0.267	0.605	4 (9.30)	2 (14.29)	0.001	0.979
Bone marrow aspiration	5 (16.13)	4 (13.79)	<0.001	>0.999	6 (13.95)	3 (21.43)	0.060	0.807
Lumbar puncture	5 (16.13)	1 (3.45)	1.453	0.228	2 (4.65)	1 (7.14)	<0.001	>0.999
Thoracentesis	2(6.45)	1(3.45)	<0.001	>0.999	2 (4.65)	0 (0)	<0.001	>0.999
Tracheotomy	11 (35.48)	19 (65.52)	5.406	0.020	3 (6.98)	7 (50.00)	10.703	0.001
Trachea cannula	10 (32.26)	15 (51.72)	2.336	0.126	3 (6.98)	5 (35.71)	5.043	0.025
Bacterial type (n, %)								
ESBL-producing strains	6 (19.35)	5 (17.24)	0.045	0.833	20 (46.51)	9 (64.29)	1.335	0.248
Carbapenem-resistant strains	6 (19.35)	19 (65.52)	13.137	<0.001	1 (2.33)	0 (0)	<0.001	>0.999
Underlying disease (n, %)								
Immune compromise	12 (38.71)	11 (37.93)	0.004	0.951	9 (20.93)	3 (21.43)	<0.001	>0.999
Cerebral vascular disease	8 (25.81)	17 (58.62)	6.638	0.010	13 (30.23)	3 (21.43)	0.087	0.768
Hypertension	11 (35.48)	11 (37.93)	0.039	0.844	16 (37.21)	4 (28.57)	0.071	0.790
Diabetes mellitus	7 (22.58)	5 (17.24)	0.267	0.605	2 (4.65)	1 (7.14)	<0.001	>0.999
Pleural effusion	6 (19.35)	6 (20.69)	0.017	0.897	10 (23.26)	3 (21.43)	<0.001	>0.999
Hypoproteinaemia	5 (16.13)	12 (41.38)	4.705	0.030	10 (23.26)	4 (28.57)	0.002	0.965
Leukaemia	5 (16.13)	8 (27.59)	1.159	0.282	6 (13.95)	3 (21.43)	0.060	0.807
Sepsis	28 (87.10)	28 (96.55)	0.201	0.654	21 (48.84)	12 (85.71)	5.892	0.015
Infection-related indices (median, IQR)								
C-reactive protein (mg/L)	139.25 (78.55, 162.84)	138.00 (74.24, 182.77)	−0.592	0.554	98.76 (75.73, 180.83)	128.33 (42.96, 211.28)	−0.102	0.919
Procalcitonin (ng/mL)	1.48 (0.87, 14.54)	4.48 (0.96, 15.14)	−0.747	0.455	2.00 (1.02, 7.04)	5.34 (2.10, 15.16)	−1.743	0.081
Disease severity (median, IQR)								
Pitt score	2.0 (1.0, 5.0)	6.0 (2.0, 8.0)	−3.364	<0.001	1.0 (0.0, 2.0)	5.0 (2.0, 9.0)	−4.237	<0.001

SOFA score	5.0 (3.0, 5.0)	9.0 (5.0, 14.0)	−4.574	<0.001	2.0 (1.0, 4.0)	9.0 (5.0, 14.0)	−3.940	<0.001
aCCI score	3.0 (2.0, 5.0)	5.0 (3.0, 7.0)	−2.506	0.012	3.0 (2.0, 4.0)	4.5 (2.5, 5.0)	−1.430	0.153
Empiric therapy (n, %)								
Third-generation cephalosporins	3 (9.68)	1 (3.45)	0.201	0.654	3 (6.98)	2 (14.29)	0.087	0.767
BLBLI	10 (32.26)	8 (27.59)	0.156	0.693	19 (44.19)	3 (21.43)	2.308	0.129
Carbapenems	15 (48.39)	15 (51.72)	0.067	0.796	15 (34.88)	4 (28.57)	0.012	0.913
Aminoglycoside	2 (6.45)	1 (3.45)	<0.001	>0.999	1 (2.33)	0 (0)	<0.001	>0.999
Inappropriate empirical therapy	9 (29.03)	19 (65.52)	8.014	0.005	5 (11.63)	7 (50.00)	7.190	0.007
Antibiotics ≥3 during hospitalization (n, %)	8 (25.81)	15 (51.72)	4.258	0.039	11 (25.58)	6 (42.86)	0.794	0.373
14-day treatment failure (n, %)	14 (45.16)	26 (89.66)	13.348	<0.001	7 (16.28)	12 (85.71)	19.896	<0.001
Length of hospital stay (mean±SD)	31.0 (22.0, 43.0)	22.0 (11.0, 31.5)	−1.501	0.133	25.0 (18.0, 34.0)	15.0 (13.0, 28.0)	−1.837	0.067

Abbreviations: ICU, intensive care unit; ESBL, extended-spectrum β-lactamase; Pitt score, Pitt bacteremia score; SOFA, sequential organ failure assessment; aCCI, age-adjusted Charlson comorbidity index; BLBLI, β-lactam-β-lactamase inhibitor.

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Table 5 ROC Analysis of Illness Severity Scores for Predicting the Prognosis of Patients with KP-HABP and E. Coli-HABP

Illness Severity Scores	AUC (95% CI)	Cut Off-value	z-Value	Youden Index J	*P*-value	Sensitivity	Specificity
Patients with KP-HABP							
Pitt (score)	0.76 (0.63–0.86)	3.0	4.24	0.40	<0.001	69.0%	71.0%
SOFA (score)	0.84 (0.72–0.92)	5.0	6.65	0.60	<0.001	72.8%	87.1%
aCCI (score)	0.69 (0.55–0.80)	5.0	2.73	0.28	0.006	41.4%	87.1%
Patients with E. coli-HABP							
Pitt (score)	0.87 (0.75–0.94)	2.0	6.02	0.60	<0.001	85.7%	74.4%
SOFA (score)	0.85 (0.73–0.93)	4.0	5.07	0.60	<0.001	78.6%	81.4%

index, the best cut-off value of the Pitt score to anticipate 30-day death in patients with E. coli-HABP was determined as 2.0. The optimal cut-off value of the SOFA score was 4.0 (Table 5), and then binary classification was performed. Next, we performed logistic regression analysis (Figure 6). Multivariate logistic regression analysis identified high SOFA score (≥ 4.0) and trachea cannula were associated significantly with 14-day treatment failure (Figure 6B). High SOFA score (≥ 4.0) and high Pitt score (≥ 2.0) were independent risk variables of 30-day mortality in patients with E. coli-HABP (all $P < 0.05$) (Figure 6D). A nomogram was further constructed based on IET, SOFA score and Pitt score (Figure 7), with predicted probabilities between 0.05–0.80 for total integrals between 48–248. Next, we validated the performance of the nomogram in patients with E. coli-HABP (Figure 8). The AUC of prediction model was 0.888 (95% CI: 0.776–0.956), with 78.6% sensitivity and 88.4% specificity (Figure 8A). The Hosmer-Lemeshow test was used to determine whether or

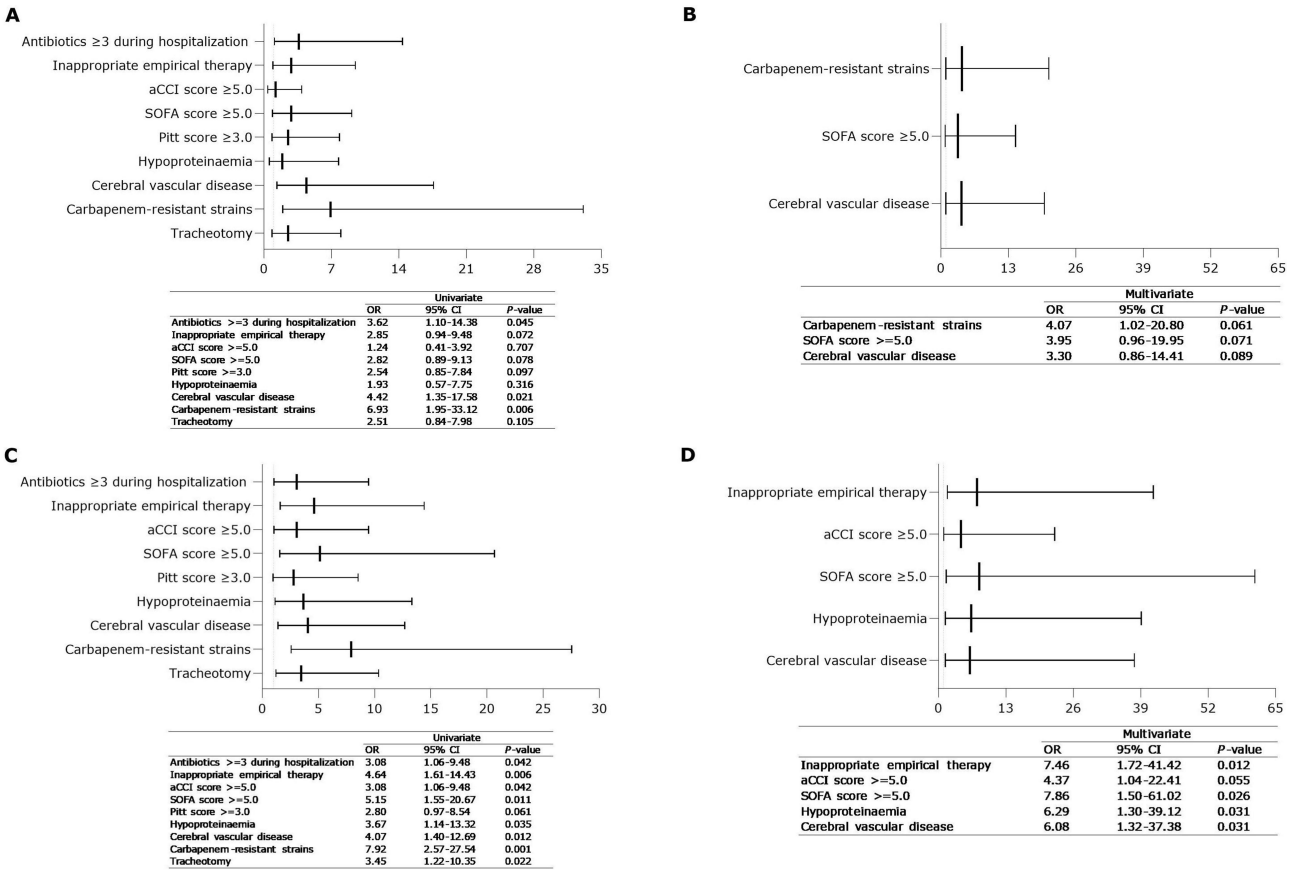


Figure 3 Logistic regression analysis for patients with KP-HABP. (**A**) Univariate logistic regression analysis was performed to evaluate the risk factors for 14-day treatment failure in patients with KP-HABP. (**B**) Multivariate logistic regression analyses were performed to evaluate the risk factors for 14-day treatment failure in patients with KP-HABP. (**C**) Univariate logistic regression analyses were performed to evaluate the risk factors for 30-day mortality in patients with KP-HABP. (**D**) Multivariate logistic regression analyses were performed to evaluate the risk factors for 30-day mortality in patients with KP-HABP.

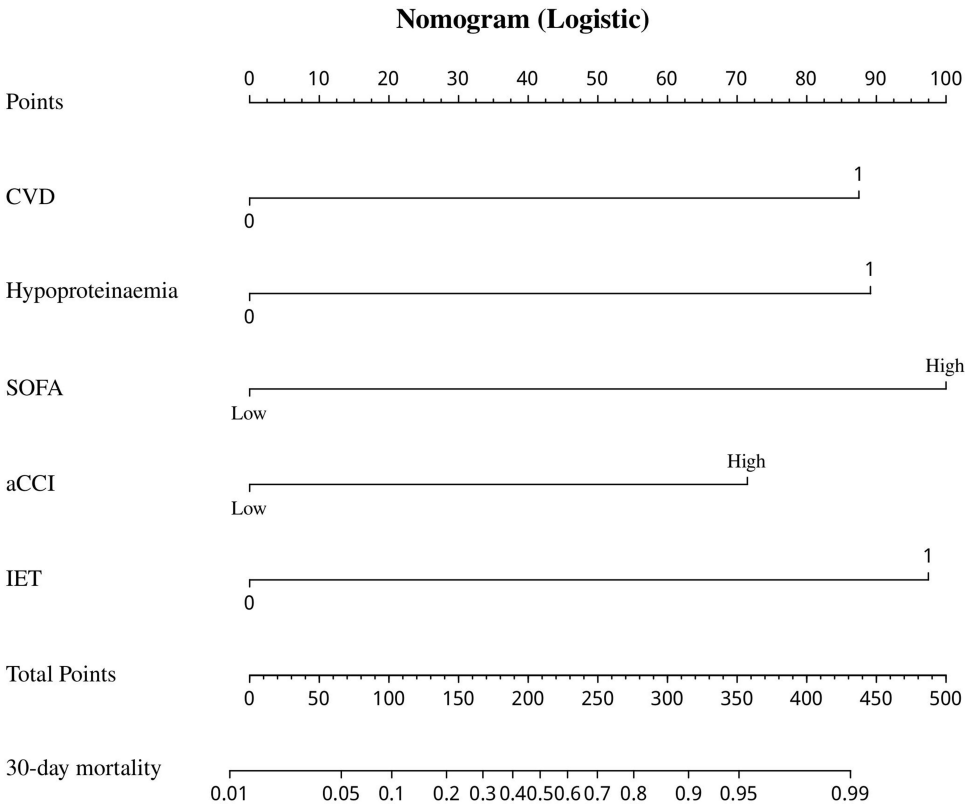


Figure 4 Nomogram for predicting the prognosis of KP-HABP patients. Nomogram, to draw an upward vertical line to the "Points" bar to calculate points. Based on the sum, draw a downward vertical line from the "Total Points" line to calculate the probability of 30-d mortality in KP-HABP for each patient.

not the regression model was a good fit yielded a significant result ($P = 0.536$), and the calibration curve demonstrated that the model prediction was consistent with the observed field data (Figure 8B). Moreover, DCA confirmed the clinical practicability of three risk factors to predict 30-d mortality in patients with E. coli-HABP (Figure 8C).

Discussion

There were significant variations in the initial clinical features of KP-HABP patients and those with E. coli-HABP. Consistent with previous reports,[31] male patients were more susceptible to KP-HABP, which may be attributed to the differences between male and female lifestyles. Epidemiological studies also found that men were generally more susceptible to infection with diverse pathogens than women.[32,33] However, further investigation is required in light of the restricted sample size. Furthermore, numerous studies confirmed that HAP is the main reason for hospital-acquired infection in the ICU.[34,35] Simultaneously, KP is mainly isolated from respiratory specimens. Some studies confirmed that *K. pneumoniae* was the most frequent reason for HAP,[36] which provided plausible explanations for our study's findings that KP-HABP patients were more frequently admitted to the ICU than E. coli-HABP patients.

Further analysis found that patients with KP-HABP had more comorbidities (immune compromise, diabetes mellitus, and sepsis) than patients with E. coli-HABP, and most patients with KP-HABP were treated with endotracheal intubation and mechanical ventilation, resulting in significantly higher disease severity (Pitt and SOFA scores) in patients with KP-HABP. It is worth noting that the extensive utilization of carbapenems has led to a significant rise in the identification of carbapenem-resistant *K. pneumoniae* (CRKP), owing to the resulting enhanced selective pressure,[37,38] combined with inappropriate empiric therapy, which significantly limits effective clinical treatment and leads to poor outcomes (14-day treatment failure and 30-day mortality). Overall, the synergy of the above factors ultimately led to higher 30-day mortality in KP-HABP patients than in E. coli-HABP patients (48.33% vs 24.56%, $P = 0.008$). The variances in pathogenesis between *K. pneumoniae* and *E. coli* necessitate an investigation into the potential impact of microbial

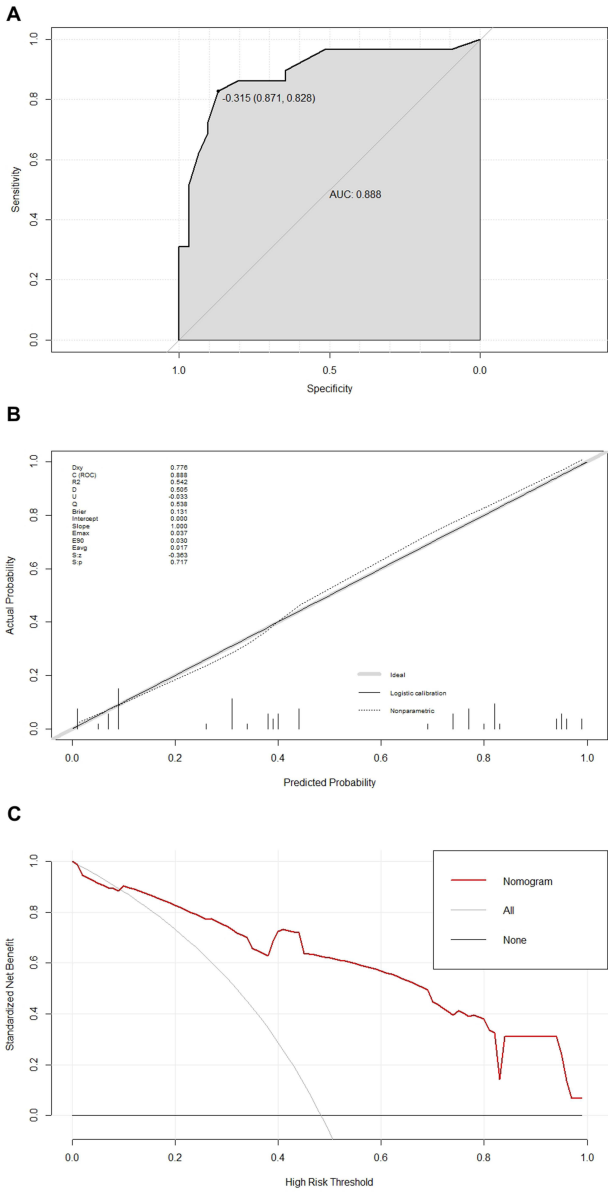
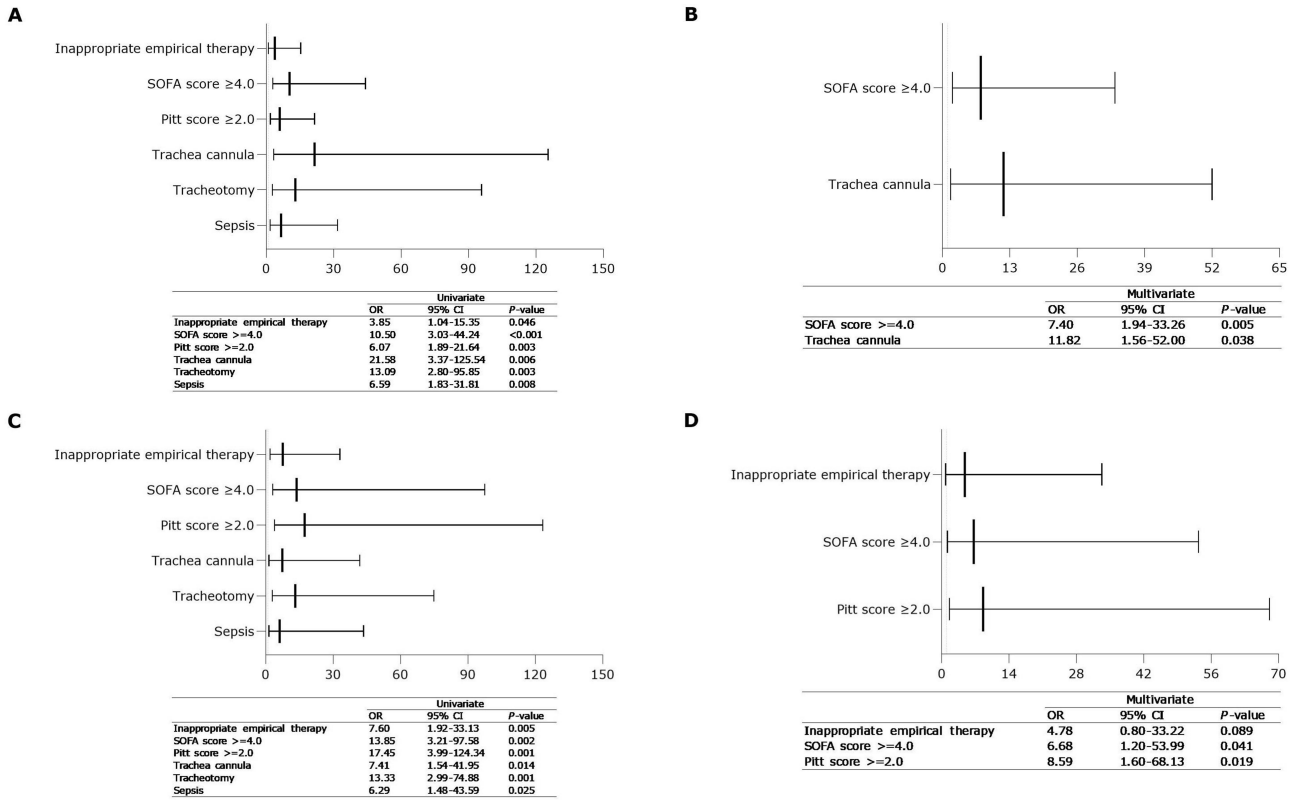


Figure 5 The validation of a predictive model for the prognosis of KP-HABP patients. (**A**) ROC curve of the prediction model for the prognosis of KP-HABP patients. (**B**) Calibration curve of the model for the prognosis of KP-HABP patients. (**C**) Clinical decision curve for the prognosis of KP-HABP patients.

type on clinical outcomes. The present study aimed to conduct a comparative analysis of the clinical outcomes of HABP in relation to microorganisms, specifically *K. pneumoniae* and *E. coli*. The findings of this study may contribute novel insights into the field of clinical diagnosis and treatment. Similar problems were described in other clinical comparative studies,[17,18,39–42] but comprehensive comparative studies of HABP caused by these two pathogens are still lacking. Although previous reports indicated no difference in short-term mortality between liver abscesses due to *E. coli* and *K. pneumoniae*,[17,42] a study found that community-onset monomicrobial bacteremia due to *E. coli* and *K. pneumoniae* had similar 28-d mortality rates (12.4% vs 14.0%, $P = 0.59$).[39] However, the results of some studies were in line with our findings. In a comparative research of community-onset *E. coli* and *K. pneumoniae* bacteremia, patients admitted with *K. pneumoniae* bacteremia exhibited elevated 30-day deaths compared to patients admitted with *E. coli* bacteremia (14.44% vs 8.8%, $P = 0.008$).[18] Moreover, acute cholangitis (AC) caused by two pathogens showed a higher 30-day mortality rate for *K. pneumoniae* infection than *E. coli* infection (20.7% vs 6.3%, $P = 0.017$).[41] Remarkably, after we found a variation in 30-day death between the two groups, KM analysis yielded similar conclusions (Figure 2) and



	Univariate		
	OR	95% CI	*P*-value
Inappropriate empirical therapy	3.85	1.04-15.35	0.046
SOFA score >=4.0	10.50	3.03-44.24	<0.001
Pitt score >=2.0	6.07	1.89-21.64	0.003
Trachea cannula	21.58	3.37-125.54	0.006
Tracheotomy	13.09	2.80-95.85	0.003
Sepsis	6.59	1.83-31.81	0.008

	Multivariate		
	OR	95% CI	*P*-value
SOFA score >=4.0	7.40	1.94-33.26	0.005
Trachea cannula	11.82	1.56-52.00	0.038

	Univariate		
	OR	95% CI	*P*-value
Inappropriate empirical therapy	7.60	1.92-33.13	0.005
SOFA score >=4.0	13.85	3.21-97.58	0.002
Pitt score >=2.0	17.45	3.99-124.34	0.001
Trachea cannula	7.41	1.54-41.95	0.014
Tracheotomy	13.33	2.99-74.88	0.001
Sepsis	6.29	1.48-43.59	0.025

	Multivariate		
	OR	95% CI	*P*-value
Inappropriate empirical therapy	4.78	0.80-33.22	0.089
SOFA score >=4.0	6.68	1.20-53.99	0.041
Pitt score >=2.0	8.59	1.60-68.13	0.019

Figure 6 Logistic regression analysis for patients with E. coli-HABP. (**A**) Univariate logistic regression analysis was performed to evaluate the risk factors for 14-day treatment failure in patients with E. coli-HABP. (**B**) Multivariate logistic regression analyses were performed to evaluate the risk factors for 14-day treatment failure in patients with E. coli-HABP. (**C**) Univariate logistic regression analyses were performed to evaluate the risk factors for 30-day mortality in patients with E. coli-HABP. (**D**) Multivariate logistic regression analyses were performed to evaluate the risk factors for 30-day mortality in patients with E. coli-HABP.

further supported our results after correction for confounders (Table 3). Indeed, our findings can be explained by the following reasons: (i) KP-HABP group had a higher number of critical illnesses on admission, along with more invasive operations during hospitalization, which resulted in a worse prognosis for KP-HABP patients. (ii) *K. pneumoniae* caused more severe bacteremia than *E. coli* in patients having severe underlying health issues, resulting to an elevated probability of death.[13,18] (iii) The higher 30-d mortality rate in patients with KP-HABP may be related to virulence factors, biofilm formation, and antimicrobial resistance of *K. pneumoniae*.[41,43] Admittedly, the small sample size limits the reliability and generalizability of results; this remains to be confirmed by a more extensive study.

Alarmingly, the rates of carbapenem resistance in *K. pneumoniae* are on the rise.[44–46] In retrospective research performed in a tertiary care hospital in China, 68.8% of patients diagnosed with HAP were identified with CRKP infection, and 25% died within 28 days.[47] Meanwhile, the data on the evolution of drug resistance of *K. pneumoniae* to imipenem and meropenem in CHINET tertiary hospitals from 2005 to 2019 showed that their resistance rates had elevated quickly from 3.0% and 2.9% in 2005 to 25.3% and 26.8% in 2019, respectively.[48] The resistance rates are on the rise, which were essentially similar to our results. Our study found that the detection rate of CRKP strains in KP-HABP patients was 41.67%, while the 30-day mortality rate was 48.33%. Moreover, a study conducted in Taiwan found that among HABP patients, the detection rate of CRKP strains, up to 58.2%, showed a 28-day death rate of 60.2%,[31] further supporting our results. Another concern was that using carbapenem antibiotics in the empirical therapy of KP-HABP patients is up to 50%, which undoubtedly increased the detection rate of CRKP strains. Therefore, the rational use of antibiotics to reduce the production of drug-resistant strains is essential to improve the prognosis of patients with KP-HABP. Besides, current studies have identified several risk factors for prognosis in patients with KP infection, including advanced age, high APACHEII score/SOFA score, infectious shock, granulocytopenia or deficiency, mechanical ventilation, central venous catheterization, insensitive anti-infective therapy.[49–53] In our study, further multiple logistic regression confirmed that inappropriate empirical therapy (IET), hypoproteinaemia, cerebral vascular disease (CVD), and

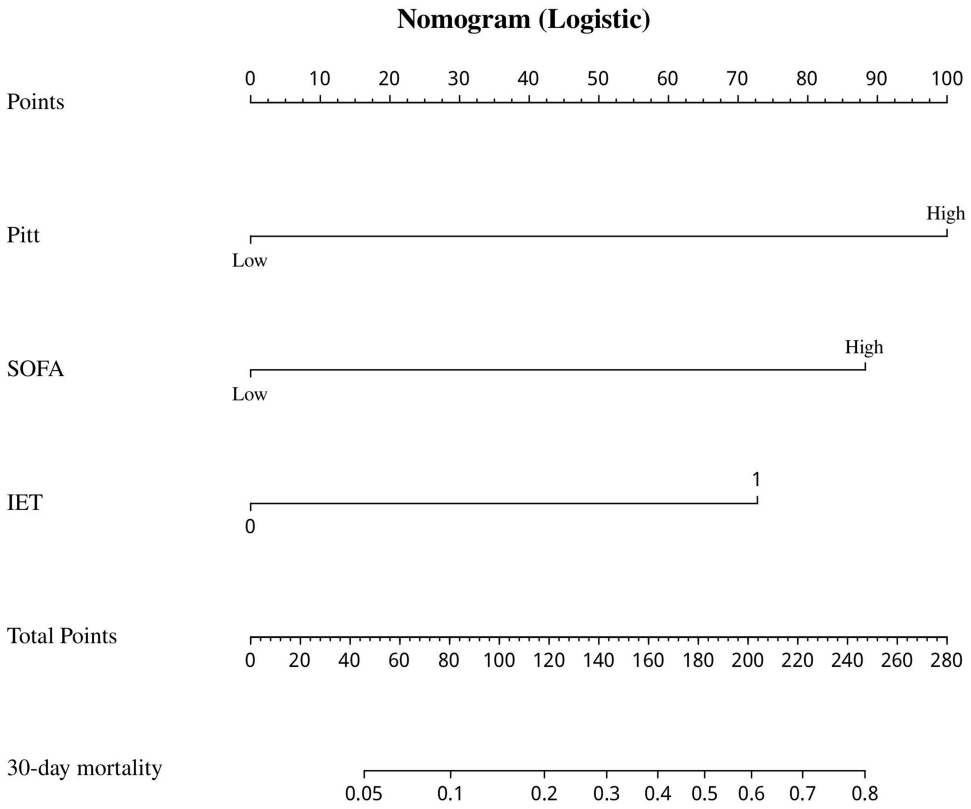


Figure 7 Nomogram for predicting the prognosis of E. coli-HABP patients.

higher SOFA score (≥ 5.0) were independent risk factors for 30-day mortality in patients with KP-HABP. Based on the potential risk factors, the constructed nomogram demonstrates good prognostic performance (Figures 4 and 5). In a word, these findings suggested that clinicians need to be alert to the risk factors associated with KP-HABP patients and that timely intervention and avoidance of disease progression are critical to improving the prognosis of patients.

Differently from patients with KP-HABP, more ESBL-producing strains were detected in E. coli-HABP patients (18.33% vs 50.88%). Combined with our drug sensitivity experiments (Table 2), most *E. coli* strains were resistant to quinolones and sulfonamides antibiotics, which may be related to the presence of multi-drug resistance genes, including quinolone and sulfonamide antibiotics on the plasmid, besides the reduced permeability of bacterial outer membrane proteins.[54] Notably, *E. coli* susceptibility to amikacin, imipenem, and piperacillin exceeded 90% in patients with E. coli-HABP. Therefore, for antibiotic selection in patients with E. coli-HABP, carbapenems can be the first choice, while amikacin and piperacillin-tazobactam can be used as alternative or combination regimens when appropriate, and quinolones and β-lactam antibiotics are not recommended, which provided a theoretical reference for clinicians to use antibiotics rationally. In parallel, E. coli-HABP patients exhibited a 30-day mortality of 24.56%. A study found a 14% hospital mortality rate in community-acquired pneumonia (CAP) caused by *E. coli*,[55] which may be due to the fact that more patients with HAP occur in the ICU and the greater chance of infection with drug-resistant bacteria. Furthermore, inappropriate empiric therapy, SOFA score ≥ 4.0, and Pitt score ≥ 2.0 were independent risk factors for 30-day mortality in patients with E. coli-HABP, which had been confirmed in previous studies.[55–57] Finally, we tried to construct the nomogram with the potential risk factors and again demonstrated good prognostic performance (Figures 7 and 8).

Limitations

There were some limitations to this study. First, this study was a single-center retrospective study, and the size of included cases was too small, which might impact on accuracy and punctuality of statistical analysis. At the same time, we did not perform sample size estimation, so the results should be interpreted and used with caution. However, due to the small number of related studies, our study still has a certain reference value. We look forward to multi-center collaboration to further confirm our findings.

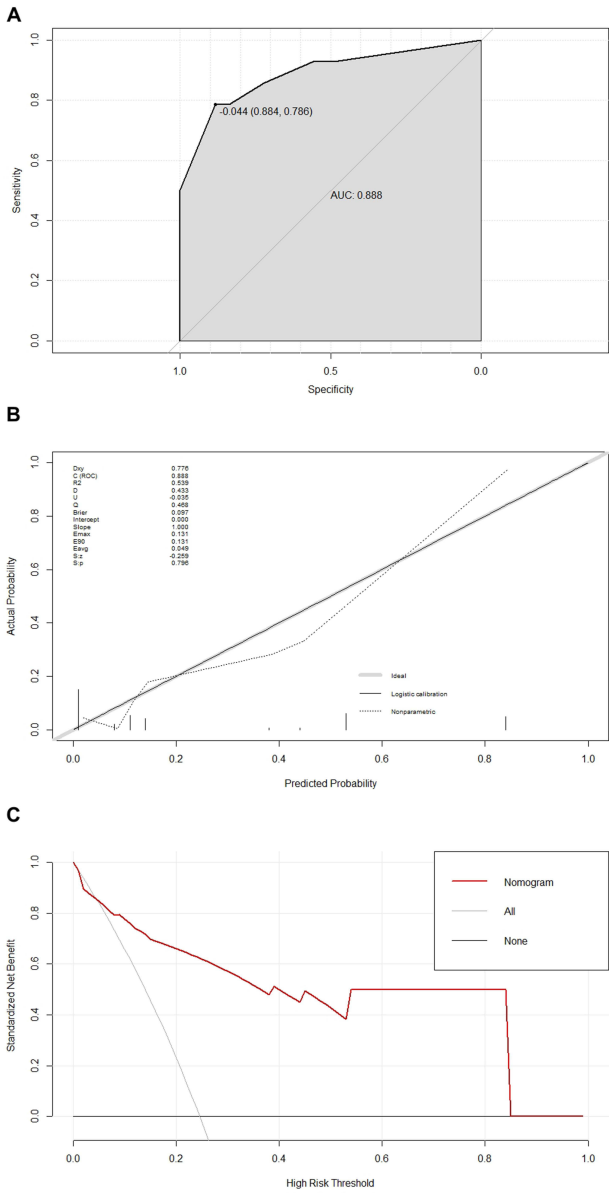


Figure 8 The validation of a predictive model for the prognosis of E. coli-HABP patients. (**A**) ROC curve of the prediction model for the prognosis of E. coli-HABP patients. (**B**) Calibration curve of the model for the prognosis of E. coli-HABP patients. (**C**) Clinical decision curve for the prognosis of E. coli-HABP patients.

Second, selection bias could not be avoided due to the retrospective study design. For example, HAP patients with undiagnosed bacteremia were not included. Third, in this study, we did not detect and analyze the molecular characteristics of drug-resistant strains so as to know the prevalence of strains causing HABP in our region. Finally, after exploring the risk factors for 30-day mortality in HABP caused by two pathogens separately, we attempted to construct a nomogram, which, although we performed internal validation, was, however, a tentative exercise and was not externally validated, which will be the focus of our subsequent study.

Conclusion

In conclusion, our study showed differences in clinical features between HABP caused by *E. coli* and *K. pneumoniae*. The 30-day mortality of HABP caused by *Klebsiella pneumoniae* was significantly higher than that of *E. coli*. Among patients with KP-HABP, inappropriate empirical therapy, hypoproteinaemia, cerebral vascular disease (CVD), SOFA score ≥ 5.0, and aCCI score ≥ 5.0 were independent risk factors for 30-day mortality. Meanwhile, inappropriate empiric

therapy, SOFA score ≥ 4.0, and Pitt score ≥ 2.0 were closely related to the prognosis of patients with E. coli-HABP. Moreover, the detection rate of carbapenem-resistant and ESBL-producing strains was high in patients with HABP, and the problem of bacterial resistance is still severe. Therefore, antimicrobial drugs should be used rationally in the clinic, and antimicrobial drugs should be selected in combination with resistance characteristics and resistance in the region.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

Informed consent was acquired from each participant included in the study. This study conformed to the guidelines of the Helsinki Declaration. Ethics approval was obtained by the Research Ethics Committee of the Second Affiliated Hospital of Nanchang University.

Consent for Publication

Written informed consent for publication was obtained from all participants.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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