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Research article

Clinical characteristics and prognosis of *Klebsiella pneumoniae* meningitis in adults

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ABSTRACT

Background: *Klebsiella pneumoniae* is a causative agent of bacterial meningitis in adults. However, there is little information regarding this infection. Therefore, this study comprehensively analyzed the clinical characteristics and prognosis of *Klebsiella pneumoniae* meningitis (KPM) patients.

Methods: The clinical data of adult hospitalized patients with KPM were retrospectively collected from January 2015 to December 2022. The clinical characteristics and antibiotic resistance of KPM were evaluated. Meanwhile, a set of logistic regression models was constructed to identify prognostic factors for death. These prognostic factors were subsequently combined to develop a nomogram for predicting the risk of in-hospital mortality in individual patients. Finally, the receiver operating characteristic curve and calibrate plot were utilized to verify the performance of the nomogram.

Results: This study included 80 adult patients with KPM, 58 (72.5%) of whom were males. The mortality rate was 45%. Among them, 74 (92.5%) were diagnosed with healthcare-associated meningitis. Thirty-seven carbapenem-resistant *Klebsiella pneumoniae* (CRKP) strains were susceptible to tigecycline, polymyxin, and ceftazidime/avibactam. CRKP (OR = 9.825, 95%CI = 2.757–35.011, P < 0.001), length of stay (OR = 0.953, 95%CI = 0.921–0.986, P = 0.005), and C-reactive protein-to-prealbumin ratio (CRP/PA, OR = 3.053, 95%CI = 1.329–7.016, P = 0.009) were identified as predictive factors for mortality using multivariate logistic regression. Finally, a nomogram for death prediction was established. The area under the curve of this nomogram was 0.900 (95% CI = 0.828–0.971).

Conclusions: KPM is a fatal disease associated with high incidence of healthcare-associated infections and carbapenem resistance. Moreover, CRKP, length of stay, and CRP/PA were found to be independent predictors of mortality.

1. Introduction

Bacterial meningitis accounts for approximately 8% of total meningitis cases, causing over 300,000 deaths worldwide annually [1]. Meningitis induced by bacterial infections contributes to high rates of disability and mortality and places a heavy burden on global health [2]. To address this issue, the World Health Organization has formulated a global roadmap to eliminate meningitis by 2030 [3].

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Among the various bacteria, *Klebsiella pneumoniae* meningitis (KPM) is gaining extensive attention due to its high resistance and mortality rates, and unfavorable prognosis [4].

Klebsiella pneumoniae (KP) is a gram-negative bacterium that can induce pneumonia, liver abscess, bacteremia, meningitis, and other infections [5]. According to drug susceptibility testing, KP can be classified into carbapenem-resistant *Klebsiella pneumoniae* (CRKP) and carbapenem-susceptible *Klebsiella pneumoniae* (CSKP). KP can also be divided into classical KP and hypervirulent *Klebsiella pneumoniae* (hvKP). Metastatic meningitis caused by hvKP mutant strains was initially described in Taiwan in 1986 [6]. A recent study highlighted fatal meningitis caused by a carbapenem-resistant hvKP variant. Characterized by hypervirulence, multiple antimicrobial resistance, and high invasiveness, this meningitis substantially threatens human health [7]. Although KP is a critical etiology of bacterial meningitis worldwide [8,9], research on KPM is inadequate. It is worth noting that healthcare-associated KPM has become increasingly prevalent [10,11]. Correspondingly, the incidence of CRKP is rapidly elevated [12]. Nevertheless, most of the literature on KPM consists of case reports. Comprehensive studies on KPM with plentiful samples are rare. Factors affecting the mortality of KPM have yet to be thoroughly investigated. It is crucial to develop an accurate and measurable prognostic model to optimize therapeutic strategies, thus achieving satisfying prognoses. Therefore, this study systematically analyzed the clinical characteristics and prognosis of KPM patients using a large sample size and comprehensive clinical information.

This retrospective study investigated the clinical characteristics and prognosis of KPM patients over eight years. Additionally, prognostic factors were identified through logistic regression. Finally, a nomogram was developed to predict the risk of in-hospital death in individual patients. These findings can provide new insights for future KPM research.

2. Materials and methods

2.1. Study population

Medical records of laboratory-confirmed KPM patients treated at the Affiliated Hospital of Xuzhou Medical University from January 2015 to December 2022 were retrospectively reviewed. Included patients met the following inclusion criteria: (1) positive cerebrospinal fluid (CSF) culture for KP; (2) clinical manifestations and/or abnormal laboratory examination results related to bacterial meningitis; (3) complete medical records; (4) age $\geq$18 years old. In this study, KPM was defined according to the 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis and the European Society of Clinical Microbiology and Infectious Diseases guidelines: diagnosis and treatment of acute bacterial meningitis [13,14]. Clinical characteristics, including symptomatology, laboratory indicators, extra infections, complications, treatments, and hospital conditions, were comprehensively analyzed. For patients with multiple episodes, only the initially documented episode was analyzed to ensure each that patient was studied only once.

To summarize the clinical characteristics of KPM, the included patients were divided into death group and survival group. Next, significant variables strongly associated with death ($P < 0.01$) were included in a multivariate logistic regression analysis to identify independent prognostic factors. Despite their P values being less than 0.01, the C-reactive protein-to-prealbumin ratio (CRP/PA) was included instead of the separate indicators of C-reactive protein and prealbumin. Only carbapenem resistance data from antibiotic resistance testing were incorporated into the multivariate logistic regression analysis. These independent prognostic factors were further employed for nomogram construction. In the validation process, discrimination capacity was assessed using the receiver operating characteristic (ROC) curve and area under the curve (AUC), and predictive precision was evaluated with calibration curves. Healthcare-associated meningitis was defined as meningitis occurring in patients under specific conditions, including CSF shunts, CSF drains, neurosurgery, or head trauma. Those without distinctive disease characteristics or invasive procedures were classified as having spontaneous meningitis.

2.2. Antimicrobial susceptibility testing

Antimicrobial susceptibility testing and determination of the minimum inhibitory concentration (MIC) were conducted for all the isolated KP strains in accordance with the European Committee on Antimicrobial Susceptibility Testing guidelines [15]. The drug resistance of the KP strains was assessed on the MIC. Multidrug resistance was defined as resistance to three or more antimicrobial agents.

2.3. Statistical analyses

For continuous data, normally distributed variables were presented as the mean $\pm$ standard deviation and variables with non-normal distribution were expressed as the median (25–75% quantiles). Differences in continuous variables were evaluated using Student's t-test. Categorical variables were presented as percentages (%). Fisher's exact test was adopted to assess the differences in categorical variables. Multivariate logistic regression analysis was also conducted to identify independent prognostic factors for death. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. $P < 0.05$ (two-tailed) was considered to indicate statistical significance in all analyses. Statistical analyses were performed with R version 4.2.1 software (Institute for Statistics and Mathematics, Vienna, Austria; http://www.r-project.org/). The "rms" package (cran. r-project. Org/web/packages/rms) was used to construct the nomogram.

3. Results

3.1. Baseline information for patients with KPM

This study included 80 patients diagnosed with KPM, 58 males and 22 females, with an average age of 52.7 ± 14.7 years. Patients were categorized into the survival group (n = 44) and the death group (n = 36) based on their prognosis. The distribution of KPM over the years is illustrated in Fig. 1A. Among the 80 KPM patients, 74 presented concomitant cranial diseases, such as cerebral hemorrhage (excluding trauma-induced or intracranial vascular malformation-related hemorrhage), head trauma, intracranial vascular malformations, benign or malignant tumors, massive cerebral infarction, and CSF leakage (Fig. 1B). Surgical interventions, including craniotomy (91.3%), lumbar cistern drainage (58.8%), external ventricular drainage (41.3%), and ventriculoperitoneal shunt (12.5%), were generally required for these patients. The baseline information for both groups is presented in Table 1.

3.2. Clinical characteristics for patients with KPM

Fever (93.8%) is the most common symptom, followed by positive meningeal irritation (62.5%). In the death group, three-quarters of the patients have a Glasgow Coma Scale (GCS) ≤ 8, with about 47.7% belonging to the survival group (P = 0.013).

Regarding CSF indicators, in contrast with those in the survival group, the polykaryocyte count is higher in the death group (2696.5×10^6/L vs. 5587.0×10^6/L, P = 0.037). Furthermore, the protein level in the death group is significantly higher than that in the survival group (P = 0.010), with medians of 11.2 (3.2, 19.2) g/L and 4.2 (2.2, 6.9) g/L, respectively. Referring to the hematological indicators, the death group displays a higher leukocyte count (P = 0.036), C-reactive protein (P = 0.002), and procalcitonin (P = 0.017) than the survival group; however, it has lower hemoglobin (P = 0.004) and prealbumin levels (P < 0.001). Moreover, the death group presents higher CSF-to-blood chloride (1.08 ± 0.11 vs. 1.14 ± 0.09, P = 0.034) and neutrophil-to-lymphocyte (NLR, 13.0 vs.

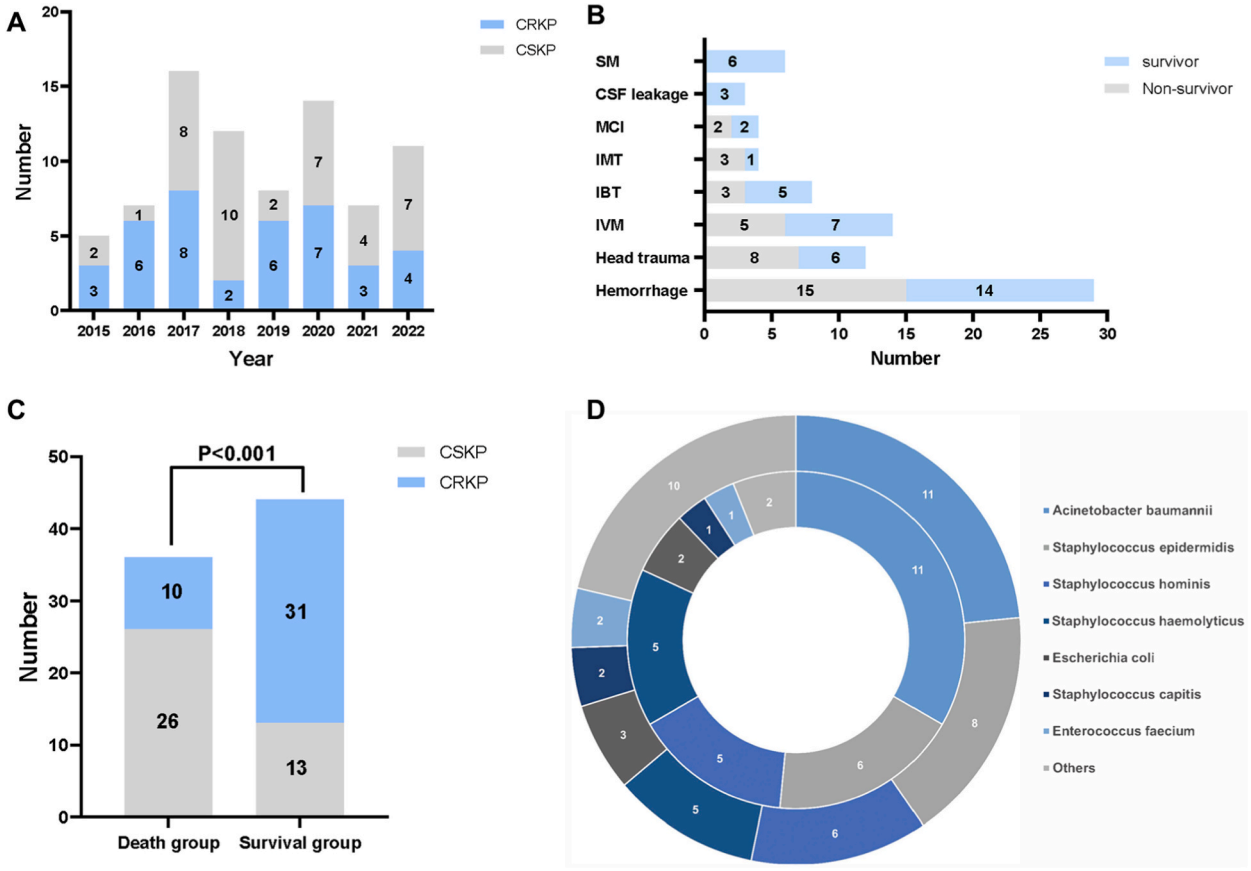

Fig. 1. Distribution of KPM patients.
Fig. 1A. Distribution of CRKP and CSKP by year; Fig. 1B. Distribution of cranial diseases of KPM; Fig. 1C. Comparison of CRKP rate in the survival group and death group (52.0% vs. 27.2%, P < 0.001); Fig. 1D. Distribution of other bacteria isolated from CSF of patients with KPM. Outer ring: Distribution of bacteria; Inner ring: Distribution of multidrug resistant bacteria. CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*; KPM, *Klebsiella pneumoniae* meningitis; SM, spontaneous meningitis; MCI, massive cerebral infarction; IMT, intracranial malignant tumor; IBT, intracranial benign tumor; IVM, intracranial vascular malformation. CSF: cerebrospinal fluid.

Table 1
Baseline table of *Klebsiella pneumoniae* meningitis.

	Total (n = 80)	Death group (n = 36)	Survival group (n = 44)	*P*-value
Demographic data				
Male, n (%)	58 (72.5)	28 (77.8)	30 (68.2)	0.339
Age (year)	52.7 ± 14.7	55.3 ± 12.1	50. 4 ± 16.4	0.108
Underlying diseases, n (%)				
Hypertension	38 (47.5)	17 (47.2)	21 (47.7)	0.964
Diabetes mellitus	13 (16.3)	6 (16.7)	7 (15.9)	0.927
liver cirrhosis	1 (1.3)	1 (2.8)	0 (0.0)	0.450
Liver abscess	1 (1.3)	0 (0.0)	1 (2.3)	1.000
Cranial diseases, n (%)				
Cerebral hemorrhage*	29 (36.3)	15 (41.7)	14 (31.8)	0.362
Head trauma	14 (17.5)	6 (16.7)	8 (18.2)	0.859
	12 (15.0)	7 (19.4)	5 (11.4)	0.314
Intracranial benign tumor	8 (10.0)	3 (8.3)	5 (11.4)	0.940
Intracranial malignant tumor	4 (5.0)	3 (8.3)	1 (2.3)	0.470
Massive cerebral infarction	4 (5.0)	2 (5.6)	2 (4.5)	1.000
CSF leakage	3 (3.8)	0 (0.0)	3 (6.8)	0.248
Cranial manipulations, n (%)				
Craniotomy	73 (91.3)	35 (97.2)	38 (86.4)	0.189
Lumbar cistern drainage	47 (58.8)	20 (55.6)	27 (61.4)	0.600
External ventricular drainage	33 (41.3)	18 (50.0)	15 (34.1)	0.150
Ventriculoperitoneal shunt	10 (12.5)	4 (11.1)	6 (13.6)	1.000

Cerebral hemorrhage*, we already ruled out hemorrhage caused by head trauma or intracranial vascular malformation; CSF, cerebrospinal fluid.

9.4, P = 0.005). The C-reactive protein-to-prealbumin ratio (CRP/PA) is greater in the death group than in the survival group (P < 0.001), with medians of 1.63 (0.81, 2.25) and 0.51 (0.22, 1.07), respectively.

For infections other than KPM, the rates of surgical incision infection, and positive blood culture with KP are 13.8% and 10.0%, respectively. The death group shows higher incidences of invasive mechanical ventilation (77.8% vs. 50.0%, P = 0.011) and positive sputum culture with KP (69.4% vs. 36.4%, P = 0.003) than the survival group. During hospitalization, 47 additional bacteria are isolated from the CSF of 26 KPM patients, for a multidrug resistance rate of 70.2%. *Acinetobacter baumannii* exhibits the highest frequency among all the other bacteria isolated from CSF during hospitalization, with a carbapenem resistance rate of up to 100%. The detailed bacterial distribution is shown in Fig. 1D. Additionally, hydrocephalus is the most common complication (21.0%), followed by epilepsy (12.5%) and septic shock (10.0%). Infectious shock (19.4% vs. 2.3%, P = 0.030) and brain abscess (13.9% vs. 0.0%, P = 0.016) are more common in the death group than in the survival group. Moreover, the survival group received more appropriate early empirical antibiotic therapy than the death group (65.9% vs. 41.7%, P = 0.030). Only six patients in this study received intrathecal injections of polymyxin or tigecycline. However, no significant therapeutic effect is observed.

The KPM category includes 74 cases of healthcare-associated meningitis and 6 cases of spontaneous meningitis. The length of stay in the death group is 18.0 (10.0, 29.0) days, which is shorter than the 33.0 (17.3, 49.8) days in the survival group (P < 0.001). The ICU stay in the death group is 10.0 (2.0, 19.0) days, which is longer compared to the 2.5 (0.0, 15.8) days in the survival group (P = 0.026). Additionally, modified Rankin Scale scores were collected at discharge to assess the quality of life of the surviving patients, with a median score of 3.5 (2, 4). Table 2 presents the specific clinical characteristics of the KPM patients.

3.3. Antibiotic resistance testing of KPs

The carbapenem-resistant rate in the death group is greater than that in the survival group (52.0% vs. 27.2%, P < 0.001; Fig. 1C). According to the extended spectrum beta-lactamase test, the positive rates were 66.7% and 38.6% (P = 0.013) in the death and survival groups. Except for piperacillin, ticarcillin, compound sulfamethoxazole, and tigecycline, the death group exhibits higher antibiotic resistance rates compared to the survival group (all P < 0.05). Two KP strains are resistant to tigecycline but susceptible to polymyxins. Moreover, 47 patients tested for polymyxin have susceptible results. Seven CRKP isolates were tested for ceftazidime/avibactam, showing susceptibility with each MIC of 21, 21, 22, 24, 26, 27, and 28 μg per milliliter. The results of antibiotic resistance testing for KPs isolated from CSF are listed in Table 3.

3.4. Risk factors for death in KPM patients

This paper assessed factors associated with mortality in KPM patients using multivariable logistic regression models. The results reveal that CRKP (OR = 9.825, 95%CI = 2.757–35.011, P < 0.001), length of stay (OR = 0.953, 95%CI = 0.921–0.986, P = 0.005), and CRP/PA (OR = 3.053, 95%CI = 1.329–7.016, P = 0.009) are predictors of in-hospital mortality. The regression models are presented in Table 4.

Table 2
Clinical characteristics of patients with *Klebsiella pneumoniae* meningitis.

	Total (n = 80)	Death group (n = 36)	Survival group (n = 44)	*P*-value
Symptomatology, n (%)				
Fever (T ≥ 38.5 °C)	75 (93.8)	35 (97.2)	40 (90.9)	0.486
Positive meningeal irritation	50 (62.5)	25 (69.4)	25 (56.8)	0.246
GCS scores ≤8	48 (60.0)	27 (75.0)	21 (47.7)	**0.013**
CSF indicators				
RBC count (10^9/L)	3.5 (1.0, 17.0)	4.0 (1.0, 12.0)	2.5 (0.0, 23.3)	0.505
WBC count (10^6/L)	3973.0 (696.8, 17304.5)	6373.0 (1018.0, 22451.0)	3013.0 (505.0, 10923.5)	0.078
Polykaryocyte count (10^6/L)	3302.4 (560.5, 15545.0)	5587.0 (849.0, 21661.0)	2696.5 (362.5, 7853.8)	**0.037**
Protein level (g/L)	5.4 (2.7, 15.0)	11.2 (3.2, 19.2)	4.2 (2.2, 6.9)	**0.010**
Blood indicators				
Leukocyte count (10^9/L)	12.7 (9.0, 17.0)	15.3 (9.7, 20.6)	11.1 (8.9, 14.2)	**0.036**
Hb (g/L)	104.0 (90.0, 116.8)	101.0 (84.0, 111.0)	110.5 (92.8, 133.8)	**0.004**
CRP (mg/L)	96.9 (45.3, 188.4)	119.6 (64.9, 200.0)	67.3 (30.9, 132.5)	**0.002**
PCT (μg/L)	1.1 (0.4, 2.9)	2.2 (0.7, 4.2)	0.7 (0.3, 2.2)	**0.017**
PA (mg/L)	110.0 (83.3, 160.0)	81.0 (56.25, 117.5)	120.5 (103.3, 175.3)	**< 0.001**
CSF/blood indicators				
Chloride ratio	1.11 ± 0.10	1.08 ± 0.11	1.14 ± 0.09	**0.034**
Glucose ratio	0.20 (0.15, 0.41)	0.20 (0.13, 0.24)	0.22 (0.15, 0.43)	0.195
Composite indicators				
PLR	266.0 (152.5, 385.6)	303.9 (160.5, 447.4)	227.0 (143.9, 332.7)	0.170
NLR	11.8 (7.3, 18.2)	13.0 (9.9, 21.6)	9.4 (5.4, 15.4)	**0.005**
CRP/PA	0.91 (0.38, 1.71)	1.63 (0.81, 2.25)	0.51 (0.22, 1.07)	**< 0.001**
Extra infections, n (%)				
Invasive mechanical ventilation	50 (62.5)	28 (77.8)	22 (50.0)	**0.011**
Sputum culture with KP	41 (51.3)	25 (69.4)	16 (36.4)	**0.003**
Other bacteria of CSF culture	26 (32.5)	8 (22.2)	18 (40.9)	0.076
Surgical incision infection	11 (13.8)	7 (19.4)	4 (9.1)	0.312
Blood culture with KP	8 (10.0)	6 (16.7)	2 (4.5)	0.155
Complications, n (%)				
Hydrocephalus	21 (26.3)	8 (22.2)	13 (29.5)	0.459
Epilepsy	10 (12.5)	4 (11.1)	6 (13.6)	1.000
Septic shock	8 (10.0)	7 (19.4)	1 (2.3)	**0.030**
Subdural empyema	6 (7.5)	4 (11.1)	2 (4.5)	0.495
Brain abscess	5 (6.3)	5 (13.9)	0 (0.0)	**0.016**
Cerebral hernia	5 (6.3)	4 (11.1)	1 (2.3)	0.246
Treatments, n (%)				
Adequate empirical antibiotic therapy	44 (55.0)	15 (41.7)	29 (65.9)	**0.030**
Intrathecal injection	6 (7.5)	4 (11.1)	2 (4.5)	0.495
Hospital conditions				
Healthcare-associated meningitis, n (%)	74 (92.5)	36 (100.0)	38 (86.4)	**0.030**
Length of stay (days)	24.5 (13.3, 42.0)	18.0 (10.0, 29.0)	33.0 (17.3, 49.8)	**< 0.001**
ICU stay (days)	6.0 (1.0, 18.0)	10.0 (2.0, 19.0)	2.5 (0.0, 15.8)	**0.026**
mRS score at discharge	3.5 (2, 4)	–	3.5 (2, 4)	–

GCS, Glasgow Coma Scale; CSF, cerebrospinal fluid; RBC, red blood cell count; WBC, white blood cell; Hb, hemoglobin; CRP, C-reactive protein; PCT, procalcitonin; PA, prealbumin; PLR, platelets -to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; CRP/PA, C-reactive protein-to-prealbumin ratio; KP, *Klebsiella pneumoniae*; ICU, intensive care unit; mRS, modified Rankin Scale.

3.5. Nomogram for predicting in-hospital death

The above-identified independent prognostic factors were used to construct a nomogram (Fig. 2A). Each variable corresponds to a value to calculate the score for each parameter. The total score was obtained by summing the points assigned to the respective factors, representing the risk of death. This nomogram can predict in-hospital death individually based on patient conditions. The prognostic model's performance was evaluated, with a yielded AUC-ROC of 0.900 (95% CI = 0.828–0.971). The ROC curve is shown in Fig. 2B. The calibrate plot indicates that the logistic regression model is well fitted (Fig. 2C).

4. Discussion

As a lethal condition, KPM heavily burdens the medical system. This study unprecedentedly carried out a comprehensive analysis of the clinical features and outcomes of KPM using the largest study sample size on this subject to date. By multivariate logistic regression analysis, mortality predictors, such as CRKP incidence, duration of hospital stay, and CRP/PA, were identified. Furthermore, nomogram to predict death in individual patients with KPM was developed for the first time.

The mortality rate of KPM in this study is 45%, which is consistent with previous reports (23.7%–62.5%) [4,16]. CRKP infection, length of stay, and CRP/PA are identified as independent risk factors for death. The nomogram was constructed based on the results of multivariate logistic regression analyses [17]. The training set's nomogram prediction achieves an AUC of 0.900. Unlike in other KPM

Table 3
Antibiotic resistance testing of *Klebsiella pneumoniae*.

	Total (n = 80)	Death group (n = 36)	Survival group (n = 44)	*P*-value
CRKP (+)	39 (48.8)	26 (72.2)	13 (29.5)	**<0.001**
ESBL (+)	41 (51.3)	24 (66.7)	17 (38.6)	**0.013**
Beta-lactam antibiotics, n (%)				
Piperacillin	71 (88.8)	35 (97.2)	36 (81.8)	0.070
Ticarcillin	75 (93.8)	35 (97.2)	40 (90.9)	0.486
Amoxicillin/clavulanic acid	53 (66.3)	31 (86.1)	22 (50.0)	**0.001**
Piperacillin/tazobactam	46 (57.5)	29 (80.6)	17 (38.6)	**< 0.001**
Cefuroxim	58 (72.5)	32 (88.9)	26 (59.1)	**0.003**
Ceftazidime	48 (60.0)	30 (83.3)	18 (40.9)	**< 0.001**
Cefepime	47 (58.8)	30 (83.3)	17 (38.6)	**< 0.001**
Aztreonam	51 (63.8)	30 (83.3)	21 (47.7)	**0.001**
Imipenem	39 (48.8)	26 (72.2)	13 (29.5)	**< 0.001**
Meropenem	39 (48.8)	26 (72.2)	13 (29.5)	**< 0.001**
Fluoroquinolones, n (%)				
Ciprofloxacin	55 (68.8)	30 (83.3)	25 (56.8)	**0.011**
Levofloxacin	52 (65.0)	29 (80.6)	23 (52.3)	**0.008**
Moxifloxacin	51 (63.8)	29 (80.6)	22 (50.0)	**0.005**
Sulfonamides, n (%)				
Compound sulfamethoxazole	35 (43.8)	19 (52.8)	16 (36.4)	0.141
Tetracyclines, n (%)				
Tetracycline	46 (57.5)	26 (72.7)	20 (45.5)	**0.016**
Tigecycline	2 (2.5)	2 (5.6)	0 (0.0)	0.199
Aminoglycosides, n (%)				
Tobramycin	50 (62.5)	27 (75.0)	23 (52.3)	**0.037**
Amikacin	26 (32.5)	16 (44.4)	10 (22.7)	**0.039**

CRKP, carbapenem-resistant *Klebsiella pneumoniae*.

Table 4
Multivariate logistics regression analysis of predictors of death in *Klebsiella pneumoniae* meningitis.

Variables	Regression coefficient	Standard error	Wald	*P*-value	Odds ratio	95% CI
CRKP	2.285	0.648	12.421	**<0.001**	9.825	2.757–35.011
Length of stay	−0.048	0.017	7.834	**0.005**	0.953	0.921–0.986
CRP/PA	1.116	0.425	6.912	**0.009**	3.053	1.329–7.016

CI, confidence interval; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRP/PA, C-reactive protein-to-prealbumin ratio.

studies, carbapenem resistance was identified as one of the risk factors for mortality [18], which can be attributed to variations in sample size and the regional genotyping of KP strains [19]. Furthermore, due to the limited use of antibiotics, patients with CRKP infections have poor prognoses. Antibiotic resistance is a challenge in the treatment of healthcare-associated infections induced by KPs [20,21]. Additionally, KP isolates exhibit resistance to antimicrobial agents through multiple mechanisms, including the production of specific enzymes, such as β-lactamases or aminoglycoside-modifying enzymes; loss of outer membrane proteins; overexpression of efflux pumps; and modification of the target antimicrobial agent [22]. The length of hospitalization is regarded as a protective factor against death. Previous studies on healthcare-associated meningitis did not reveal a significant difference in the length of hospitalization between death and survival groups [23]. The longer the length of hospitalization is, the more stable the patient's condition tends to be. KPM is a highly aggressive infection that can provoke fatal outcomes rapidly. Furthermore, CRP/PA levels can serve as sensitive indicators of inflammation severity and immunity status, which are associated with poor prognosis [24]. However, few studies have reported the relationship between KPM and CRP/PA. In future clinical practice, it may serve as a novel predictive factor.

Healthcare-associated meningitis accounts for 92.5% of KPM cases. The prevalence of healthcare-associated KPM steadily rises from 18.2% to 93.8% [4,20]. This difference may be attributed to the greater incidence of head trauma and craniofacial surgeries. KPM is more prevalent in males than in females [18], possibly due to the higher incidence of specific cranial diseases in men than in women. KP can directly infect the CNS through cranial notches or enter the bloodstream from primary infection sites, such as the lungs, liver, or urinary tract, thus inducing meningitis. Its pathogenesis involves adhesion, invasion, inflammatory response, immune cell activation, and subsequent damage to neurological tissues [5]. Risk factors for KP infection include pathogen characteristics, host factors, external factors, and others [25]. During the hospitalization of KPM patients, carbapenem-resistant *Acinetobacter baumannii* is the most common bacteria in CSF and synergistically affects KP [26]. The six patients with spontaneous KPM in this study are consistent with existing research, possessing sensitivity to third-generation cephalosporins and high invasiveness. Additionally, this study reported an optimized prognosis for these patients [27]. These better outcomes may be attributed to a high awareness of KPM and early initiation of sensitive antimicrobial therapy.

Empiric therapy for spontaneous meningitis should include a third or fourth-generation cephalosporin, while carbapenems and vancomycin are considered the first-line treatments for postcranial surgical infection [13,14]. This study recommended tigecycline, polymyxins, and ceftazidime/avibactam for the treatment of CRKP infection [28–30]. In 1976, the initiation of intrathecal amikacin

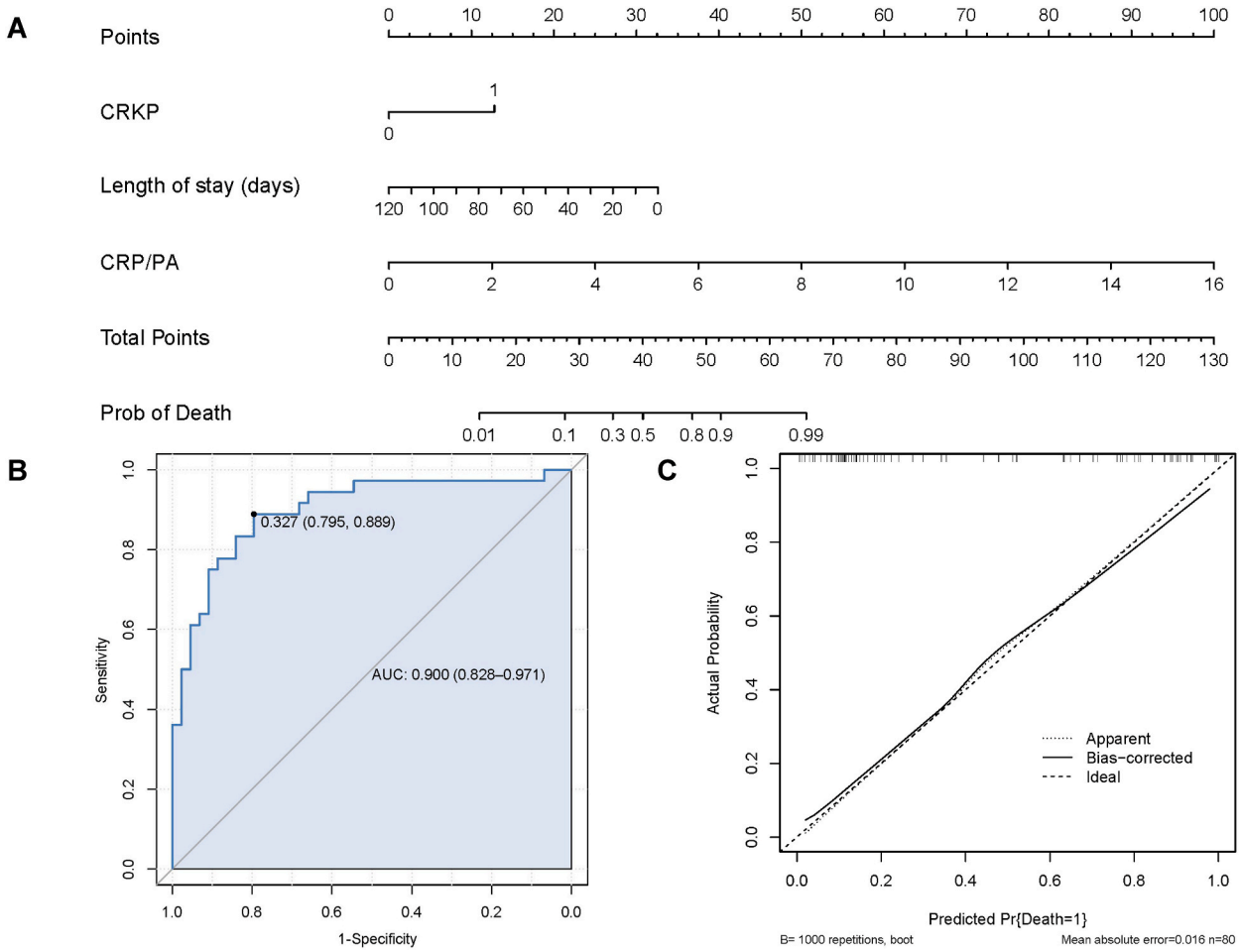

Fig. 2. A nomogram for KPM patients.
Fig. 2A. A nomogram for predicting in-hospital mortality in KPM patients; Fig. 2B. ROC curve of the nomogram for predicting death in KPM patients. The AUC of the ROC curve was 0.864 (95% CI, 0.779–0.948); Fig. 2C. Calibration curves for death in KPM patients. KPM, *Klebsiella pneumoniae* meningitis. CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRP/PA, C-reactive protein-to-prealbumin ratio; ROC, receiver operating characteristic; AUC, area under curve.

for KPM treatment bypassed the blood-CSF barrier and directly delivered antimicrobial agents to the infection site [31]. In another study, combining intravenous and intrathecal antibiotic injections provided satisfying results [32]. Refining administration techniques, monitoring CSF drug concentrations, and performing comprehensive safety analyses should be implemented to achieve desirable outcomes. Given the limitations of traditional culture methods, the rapid diagnosis of CSF pathogens is crucial for infection control. Metagenomic next-generation sequencing of CSF has been applied in the clinic [33]. However, the high cost constrains its routine use. In Taiwan, an approved immunochromatographic test can directly detected the K1/K2 serotype of KPM [34]. Furthermore, a highly specific and sensitive reaction-based diagnostic tool, a multiplex polymerase chain, has been developed for hvKP identification [35]. To achieve rapid, accurate, and cost-effective diagnosis of CSF pathogens, multifaceted measures are essential, including enhancing existing methodologies, exploring novel diagnostic techniques, and ensuring the accessibility of diagnostic instruments. Considering the urgency of addressing CRKP, it is of enormous importance to execute effective infection control and monitoring strategies worldwide [36]. The significance of plasmid analysis in monitoring the emergence of carbapenem-resistant and hypervirulent strains of KP has been highlighted [37]. Ongoing research on *Klebsiella* vaccines has verified their potential for preventing neonatal sepsis and mortality [38]. However, further validation is necessary to determine their effectiveness in managing adult KPM. Finally, strict adherence to efficacious isolation practices and proper hand hygiene are paramount to avert the spread of KP.

This study analyzed the clinical characteristics and prognosis of KPM patients in a Chinese hospital in detail. Furthermore, three prognostic factors for patients with KPM after admission were successfully identified. Of note, this study is the first to develop a nomogram model for predicting in-hospital mortality among KPM patients. It stands out as one of the largest studies on this topic. However, there are several shortcomings. First, because of the retrospective nature of this study and single-center design, the potential bias of selection and information confines the generalizability of the findings. Second, due to resource limitations, further experiments including molecular subtyping, virulence-associated genotyping, and antibiotic-resistance genotyping, were not performed on CSF-

isolated KP strains. The isolates have not been characterized regarding the probable hypervirulent phenotype, which may affect prognosis. Third, additional bacteria isolated from CSF, particularly carbapenem-resistant *Acinetobacter baumannii*, may have biased the results to some extent. Fourth, although our sample size is larger than that of most studies on KPM, the sample size is still insufficient. Internal and external validation sets are crucial to verify the nomogram's performance and generalizability.

5. Conclusion

To sum up, KPM is a disease with high mortality and KP exhibits a high rate of carbapenem resistance. CRKP, short hospitalization, and elevated CRP/PA are independent prognostic factors for mortality. The nomogram model has substantial potential for predicting the prognosis of patients with KPM. Future studies with prospective and multicenter designs and adequate sample sizes are imperative to demonstrate these findings.

6. Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Ethics approval

This study received approval by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Approval No. XYFY-2023-K313). Given its retrospective nature and absence of study-related interventions, informed consent of individual patient was waived by the ethics committee.

CRediT authorship contribution statement

Xin Yang: Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Yanjun Wang:** Methodology, Data curation. **Siqi Zhao:** Formal analysis, Data curation. **Xiaoya Huang:** Formal analysis, Data curation. **Bingxin Tian:** Formal analysis, Data curation. **Runli Yu:** Data curation. **Qin Ding:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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