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Original Article

Multivariate regression reveals linear correlation between ICU *Klebsiella pneumoniae* resistance and antibiotic use

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Abstract

Introduction: This study investigated the macro-quantitative correlation between *Klebsiella pneumoniae* resistance rates and concurrent antimicrobial use in the intensive care unit (ICU), to guide treatment for chronic refractory infections caused by this pathogen, by optimizing outcomes for critically ill patients while curbing bacterial resistance spread or transmission.

Methodology: A retrospective analysis was conducted on the resistance rate of *K. pneumoniae* and the concurrent use of antimicrobial agents in the ICU. A multiple linear regression model was employed to analyze whether there was an independent linear correlation between the two, and to identify the relevant factors.

Results: 936 *K. pneumoniae* isolates were identified in the ICU between 2020 and 2024, representing 20.45% (936/4,577) of all bacterial isolates recovered from the ICU. The resistance rates to most antimicrobial agents, except for tigecycline and trimethoprim-sulfamethoxazole, exceeded 65%, indicating a severe resistance situation. Multiple linear regression analysis revealed that the resistance rates of *K. pneumoniae* to imipenem, piperacillin-tazobactam, and ceftazidime were independently linear correlated only with piperacillin-tazobactam defined daily doses (DDDs), with regression coefficients (β) of 0.221, 0.224, and 0.166, respectively. The resistance rates to ceftriaxone, cefoperazone-sulbactam, and ertapenem were positively correlated with piperacillin-tazobactam DDDs. Resistance to cefepime was positively correlated with ceftazidime DDDs. Resistance to tigecycline was positively correlated with meropenem DDDs. Resistance to levofloxacin was negatively correlated with cefoperazone-sulbactam DDDs.

Conclusions: The resistance rate of *K. pneumoniae* in the ICU is closely related to antimicrobial use. Hospitals should strengthen the regulation of antimicrobial use to delay the emergence of drug-resistant species.

Key words: intensive care unit; *Klebsiella pneumoniae*; multiple linear regression analysis; linear correlation.

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Introduction

Klebsiella pneumoniae, a Gram-negative bacterium belonging to the family Enterobacteriaceae, represents the most clinically significant species in the *Klebsiella* genus, and is responsible for 95% of all *Klebsiella*-related infections [1]. *K. pneumoniae* is recognized as a leading cause of nosocomial infections, and particularly threatens immunocompromised individuals, critically ill patients in intensive care units (ICU), and elderly populations, necessitating heightened surveillance in hospital settings. *K. pneumoniae* can cause bloodstream infections, pneumonia, urinary tract infections, and intra-abdominal infections in ICU patients. Severe manifestations include sepsis or purulent meningitis, both linked to significant mortality [2,3].

Patients in the ICU are typically critically ill, immunocompromised, and frequently subjected to invasive procedures, making them more susceptible to bacterial infections and healthcare-associated infections [4]. The prevalence and mortality in the ICU patients that are attributable to *K. pneumoniae* are significantly higher than in other departments, with gut colonization of drug-resistant species being a major source of hospital-acquired infections [5]. The presence of *K. pneumoniae* in ICUs is rising, causing higher mortality and increased risks of septic shock or multi-organ dysfunction in patients [6]. Hypervirulent *K. pneumoniae* (HvKP) is characterized by hypermucoviscosity, rapid disease progression, and poor prognosis [7]; resulting in treatment failure and prolonged clinical courses. In recent years, the infection and resistance rates of *K. pneumoniae* in the ICU have

been rising [8], with related infections causing prolonged illness and substantially compromising to clinical antimicrobial therapy.

ICU patients are at high risk for multidrug-resistant bacterial infections and transmission [9]. Current studies on *K. pneumoniae* resistance and antimicrobial use correlations predominantly rely on hospital-wide data, with notably limited ICU-specific research, often yielding contradictory findings. Further investigation is needed to determine whether hospital-derived resistance patterns can be extrapolated to critically ill ICU patients. Specialist clinical units highlight tailored analyses. This 5-year retrospective study investigated the association between *K. pneumoniae* resistance and antimicrobial usage in ICUs, with the aim to optimize treatment strategies and contain resistance development in high-risk patients.

Methodology

Source of strain

K. pneumoniae isolates were collected aseptically from ICU patients at the hospital between 2020 and 2024. The isolates were obtained from sputum, throat swabs, bronchoalveolar lavage fluid, blood, urine, pleural effusion, peritoneal fluid, and drainage specimens. Cultivation followed the National Clinical Laboratory Procedures Manual (Fourth Edition) [10]. Only the initial susceptibility result was included in the case of recurrent isolates from identical patient specimens. Colonizing or contaminating species were excluded based on clinical presentation, susceptibility profiles, and treatment response. *K. pneumoniae* ATCC700603 from the National Clinical Laboratories Center was used for quality control. The study was approved by the Hospital Ethics Committee (2023–K046).

Isolate identification and antimicrobial susceptibility testing

Susceptibility testing was performed using the Kirby-Bauer disk diffusion method. Bacterial identification and susceptibility testing were conducted with the VITEK-2 system (BioMérieux, Craponne, France) and its associated reagents, while excluding repeated isolates from the same patient site. The results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI), 2024 (M100-S34) [11]. The specimens were collected and tested by the hospital's bacteriology lab, and data were compiled and communicated by the infection control department.

Usage of antibacterial drugs

The World Health Organization (WHO) defined daily dose (DDD) serves as the standard reference for calculating the consumption of antimicrobial agents in DDD units. DDDs quantify the prescribing frequency, with higher values indicating stronger clinical preference for an agent. The formula used for calculation was as follows:

DDDs = annual total consumption of the drug / DDD value of the drug

Table 1. Detection of *K. pneumoniae* in ICU.

	ICU *K. pneumoniae* count / isolates	Total bacterial count isolated from ICU / isolates	Total number of *K. pneumoniae* isolates in the hospital / isolates	Percentage of *K. pneumoniae* among total ICU isolates / %	Proportion of ICU *K. pneumoniae* isolates among total hospital isolates / %
Q1 2020	16	142	65	11.27	24.62
Q2 2020	25	192	76	13.02	32.89
Q3 2020	25	150	92	16.67	27.17
Q4 2020	32	216	104	14.81	30.77
Q1 2021	41	201	121	20.40	33.88
Q2 2021	42	273	142	15.38	29.58
Q3 2021	42	276	157	15.22	26.75
Q4 2021	51	271	132	18.82	38.64
Q1 2022	52	298	124	17.45	41.94
Q2 2022	38	244	126	15.57	30.16
Q3 2022	39	232	132	16.81	29.55
Q4 2022	32	231	141	13.85	22.70
Q1 2023	40	231	135	17.32	29.63
Q2 2023	74	270	195	27.41	37.95
Q3 2023	67	185	146	36.22	45.89
Q4 2023	86	298	215	28.86	40.00
Q1 2024	68	249	155	27.31	43.87
Q2 2024	59	180	162	32.78	36.42
Q3 2024	57	208	153	27.40	37.25
Q4 2024	50	230	161	21.74	31.06
Total	936	4577	2734	20.45	34.24

ICU: intensive care unit; *K. pneumoniae*: *Klebsiella pneumoniae.*

Table 2. DDDs of commonly used antibiotics in ICU.

	TZP	CFS	CAZ	CFX	AZT	IPM	MEM	GEN	LVX	TGC	CMS	OMT
Q1 2020	6.11	304.00	204.00	3.33	2.75	69.00	168.00	0.00	91.00	77.50	0.00	0.00
Q2 2020	8.36	303.75	177.25	28.33	0.00	66.50	344.75	14.00	26.00	139.00	0.00	0.00
Q3 2020	36.96	498.50	213.25	2.00	20.25	50.50	391.50	0.00	43.00	101.50	0.00	0.00
Q4 2020	27.00	420.50	126.25	25.17	0.00	27.50	242.25	0.00	68.00	40.50	0.00	0.00
Q1 2021	3.54	383.50	131.25	27.00	0.00	19.00	305.50	0.00	64.00	146.00	0.00	0.00
Q2 2021	8.04	560.00	159.00	6.00	0.00	17.00	362.25	12.67	45.00	111.50	0.00	0.00
Q3 2021	81.64	410.25	111.25	57.67	9.375	40.25	292.50	0.67	33.00	122.00	0.00	0.00
Q4 2021	131.14	114.75	68.50	55.83	60.25	8.25	330.75	20.33	55.00	119.00	0.00	0.00
Q1 2022	121.50	271.00	129.00	23.00	35.00	16.50	459.50	4.67	76.00	131.50	0.00	0.00
Q2 2022	133.71	317.50	123.25	70.33	0.00	11.00	180.50	6.33	67.00	116.50	0.00	0.00
Q3 2022	130.18	211.25	45.75	56.50	0.00	0.00	271.00	0.00	40.00	0.00	0.00	0.00
Q4 2022	189.00	415.75	61.50	44.00	25.50	29.75	312.00	1.33	75.00	16.50	0.00	0.00
Q1 2023	124.07	525.50	95.50	65.83	0.00	31.75	178.00	0.00	48.00	56.00	0.00	0.00
Q2 2023	148.50	325.75	139.00	6.50	0.00	4.50	154.50	12.67	46.00	43.00	0.00	13.00
Q3 2023	174.21	494.50	161.75	8.83	0.00	18.75	75.00	8.00	28.00	115.00	0.00	23.00
Q4 2023	105.75	262.00	162.00	20.67	13.00	8.00	195.75	0.00	70.00	90.50	0.00	4.00
Q1 2024	165.86	272.50	216.25	8.33	2.00	15.00	175.50	0.00	24.00	95.00	0.00	0.00
Q2 2024	150.43	232.75	116.00	0.00	0.00	27.00	223.25	0.00	17.00	134.00	3.00	14.00
Q3 2024	183.21	241.75	100.50	0.00	0.00	22.25	213.25	0.00	60.00	63.50	162.50	49.00
Q4 2024	101.57	278.75	137.00	0.00	10.00	34.75	260.00	0.00	41.00	30.00	87.00	17.00

DDD: defined daily dose; ICU: intensive care unit; TZP: piperacillin/tazobactam; CFS: cefoperazone/sulbactam; CAZ: ceftazidime; CFX: cefoxitin; AZT: aztreonam; IPM: imipenem; MEM: meropenem; GEN: gentamicin; LVX: levofloxaci; TGC: tigecycline; CMS: colistimethate sodium; OMT: omadacycline tosylate.

Table 3. Resistance of *K. pneumoniae* in the ICU.

	TZP	CRO	CAZ	FEP	CFS	ETP	IPM	AMK	SXT	LVX	TGC
Q1 2020	31.2	62.5	50.0	90.0	/	/	25.0	/	/	71.4	0
Q2 2020	20.0	48.0	44.0	100.0	/	/	24.0	/	/	87.5	4.2
Q3 2020	43.5	47.8	43.5	66.7	44.4	50.0	30.4	33.2	10.0	66.7	0
Q4 2020	34.4	41.9	28.1	40.6	33.3	32.3	28.1	18.8	18.8	65.6	3.2
Q1 2021	53.7	53.7	53.7	53.7	48.5	44.7	46.3	31.7	39.0	51.2	0
Q2 2021	52.4	52.6	50.0	57.1	50.0	44.7	40.5	38.1	42.9	47.6	0
Q3 2021	66.7	78.0	66.7	76.2	68.3	61.0	59.5	35.7	35.7	73.8	0
Q4 2021	68.6	75.5	64.7	72.5	66.7	63.3	64.7	37.3	47.1	76.5	0
Q1 2022	69.2	71.4	44.2	67.3	65.4	67.3	67.3	50.0	21.2	73.1	5.8
Q2 2022	73.7	73.7	65.8	71.1	71.8	73.7	68.4	44.7	21.1	73.7	0
Q3 2022	46.2	56.8	48.7	51.3	43.6	43.2	41.0	23.1	23.1	53.8	2.6
Q4 2022	59.4	59.4	50.0	46.9	43.8	50.0	50.0	31.3	15.6	56.3	0
Q1 2023	56.4	57.5	55.0	57.5	51.3	50.0	60.0	32.5	30.0	52.5	0
Q2 2023	69.0	72.1	73.0	71.6	68.9	64.7	66.2	58.1	32.4	67.6	0
Q3 2023	79.1	84.8	76.1	77.6	77.6	75.8	74.6	65.7	38.8	76.1	0
Q4 2023	84.9	87.3	86.0	83.7	79.1	80.3	76.7	62.8	44.2	81.4	0
Q1 2024	86.8	93.8	86.8	82.4	79.4	81.3	82.4	66.2	50.0	83.8	0
Q2 2024	81.4	/	83.1	79.7	72.9	/	71.2	65.5	39.0	78.0	0
Q3 2024	82.5	/	87.7	84.2	71.9	/	66.7	55.4	40.4	86.0	0
Q4 2024	66.0	/	68.0	76.0	64.0	/	56.0	32.0	30.6	65.3	0

ICU: intensive care unit; *K. pneumoniae*: *Klebsiella pneumoniae;* TZP: piperacillin/tazobactam; CRO: ceftriaxone; CAZ: ceftazidime; FEP: cefepime; CFS: cefoperazone/sulbactam; ETP: ertapenem; IPM: imipenem; AMK: amikacin; SXT: trimethoprim/sulfamethoxazole; LVX: levofloxacin; TGC: tigecycline.

Table 4. Correlation between resistance rates of *K. pneumoniae* in ICU (columns) and antibiotic DDDs (rows).

	TZP	CFS	CAZ	CFX	AZT	IPM	MEM	GEN	LVX	TGC	CMS	OMT
KP-TZP	0.759[b]	- 0.269	- 0.127	- 0.091	0.122	- 0.629[b]	- 0.354	- 0.082	- 0.179	0.116	0.271	0.454[a]
KP-CRO	0.647[b]	- 0.371	0.119	- 0.004	0.173	- 0.422	-0.451	0.061	- 0.162	0.205	-	0.401
KP-CAZ	0.625[b]	- 0.364	0.059	- 0.243	- 0.113	- 0.367	- 0.558 [a]	- 0.054	- 0.339	0.122	0.379	0.578[b]
KP-FEP	0.038	- 0.395	0.498[a]	- 0.343	- 0.061	0.381	- 0.235	0.184	- 0.264	0.418	0.238	0.321
KP-CFS	0.552[a]	- 0.424	0.278	- 0.206	0.016	- 0.293	- 0.458	0.183	- 0.311	0.412	0.196	0.411
KP-ETP	0.596[a]	- 0.373	0.377	- 0.111	0.136	- 0.323	- 0.406	0.183	- 0.189	0.391	-	0.397
KP-IPM	0.777[b]	- 0.289	- 0.138	0.032	0.130	- 0.632[b]	- 0.393	0.010	- 0.216	0.152	0.147	0.354
KP-AMK	0.539	- 0.244	0.431	- 0.464	- 0.127	- 0.295	- 0.468	0.119	- 0.330	0.396	0.091	0.438
KP-SXT	0.127	- 0.299	0.156	- 0.234	- 0.048	- 0.386	- 0.340	0.294	- 0.381	0.390	0.177	0.277
KP-LVX	0.268	- 0.522[a]	0.329	- 0.238	0.101	0.161	- 0.213	0.129	- 0.199	0.360	0.258	0.372
KP-TGC	- 0.210	- 0.174	- 0.065	0.098	0.122	0.088	0.502[a]	0.110	0.104	0.066	- 0.152	- 0.236

[a]$p < 0.05$, [b]$p < 0.01$; ICU: intensive care unit; *K. pneumoniae*: *Klebsiella pneumoniae;* KP: *Klebsiella pneumoniae*; DDD: defined daily dose; TZP: piperacillin/tazobactam; CFS: cefoperazone/sulbactam; CAZ: ceftazidime; CFX: cefoxitin; AZT: aztreonam; IPM: imipenem; MEM: meropenem; GEN: gentamicin; LVX: levofloxacin; TGC: tigecycline; CMS: colistimethate sodium; OMT: omadacycline tosylate; CRO: ceftriaxone; FEP: cefepime; ETP: ertapenem; AMK: amikacin; SXT: trimethoprim/sulfamethoxazole.

Data analysis

Data analysis was performed using SPSS 23.0 software (IBM Corporation, Armonk, NY). Pearson correlation analysis was conducted between the resistance rates of ICU *K. pneumoniae* and the DDDs of antimicrobial agents (significance level $\alpha = 0.05$). Multiple linear regression was conducted to further assess independent, linear, and significant factors in the observed correlations, as well as the impact of independent variables on the dependent variable. The model incorporated ICU *K. pneumoniae* resistance rates as the dependent variable and the antimicrobial DDDs demonstrating statistical significance in Pearson correlation analysis as independent variables. A stepwise selection approach was implemented for variable screening. The assumptions included linearity, normally distributed independent residuals, homoscedasticity, and no multicollinearity.

Results

Detection of K. pneumoniae in the ICU

A total o f 4,577 bacterial species were isolated in the ICU between 2020 and 2024, of which 936 were *K. pneumoniae*, accounting for 20.45% (936/4,577) of all bacterial isolates recovered ICU-wide. Additionally, among the 2,734 *K. pneumoniae* isolates recovered hospital-wide, ICU isolates accounted for 34.24% (936/2,734). Both horizontal and longitudinal comparisons showed a significant increase in the detection rate of *K. pneumoniae* species in the ICU (Table 1). Besides, among the 936 isolates of *K. pneumoniae* isolated in the ICU, 620 species were from respiratory specimens (including sputum and bronchoalveolar lavage fluid), accounting for 66.24%, followed by urine specimens (114 isolates, 12.18%), and blood specimens (53 isolates, 5.66%). These results indicate that the respiratory tract is a high-risk site for *K. pneumoniae* infections in the ICU.

Usage of antibacterial drugs

The use of antibiotics in the ICU was dominated by beta lactams from 2020 to 2024, and the top three DDDs in terms of frequency of use were cefoperazone-sulbactam, meropenem, and cefotaxime. The DDDs of the commonly used antibiotics in the ICU is detailed in Table 2.

Drug resistance of K. pneumoniae in the ICU

The overall resistance rate of *K. pneumoniae* isolated from ICU was relatively high, with resistance rates to most antibiotics exceeding 65%, indicating a dire situation of drug resistance. In the past 5 years, the resistance rate of *K. pneumoniae* in the ICU to piperacillin-tazobactam, cefoperazone-sulbactam, ertapenem, and imipenem had increased significantly (Table 3).

Pearson correlation analysis

Pearson correlation analysis revealed that the resistance rates of *K. pneumonia*e in the ICU to imipenem, piperacillin-tazobactam, and ceftazidime correlated with DDDs of multiple antibiotics; resistance to ceftriaxone, cefoperazone-sulbactam, cefepime, ertapenem, tigecycline, and levofloxacin each

Table 5. Linear regression analysis.

model	Dependent variable	Independent variable	Unstandardized coefficients		Standardized coefficients	t (*p*)	95% confidence interval forβ		R^2	F	VIF
			β	Standard error			lower limit	upper limit			
1	KP-IPM	TZP-DDDs	0.221	0.042	0.777	5.240 (0.000)	0.132	0.309	0.604	27.460	1.000
2	KP-TZP	TZP-DDDs	0.224	0.045	0.759	4.950 (0.000)	0.129	0.319	0.577	24.507	1.000
3	KP-CAZ	TZP-DDDs	0.166	0.049	0.625	3.395 (0.003)	0.063	0.269	0.390	11.524	1.000
4	KP-FEP	CAZ-DDDs	0.160	0.066	0.498	2.438 (0.025)	0.022	0.298	0.248	5.945	1.000
5	KP-CFS	TZP-DDDs	0.135	0.051	0.552	2.648 (0.018)	0.027	0.243	0.305	7.013	1.000
6	KP-ETP	TZP-DDDs	0.149	0.056	0.596	2.679 (0.019)	0.029	0.269	0.356	7.176	1.000
7	KP-CRO	TZP-DDDs	0.151	0.046	0.647	3.284 (0.005)	0.053	0.249	0.418	10.787	1.000
8	KP-TGC	MEM-DDDs	0.009	0.004	0.502	2.465 (0.024)	0.001	0.017	0.252	6.076	1.000
9	KP-LVX	CFS-DDDs	- 0.053	0.021	- 0.522	- 2.600 (0.018)	-0.096	-0.010	0.273	6.758	1.000

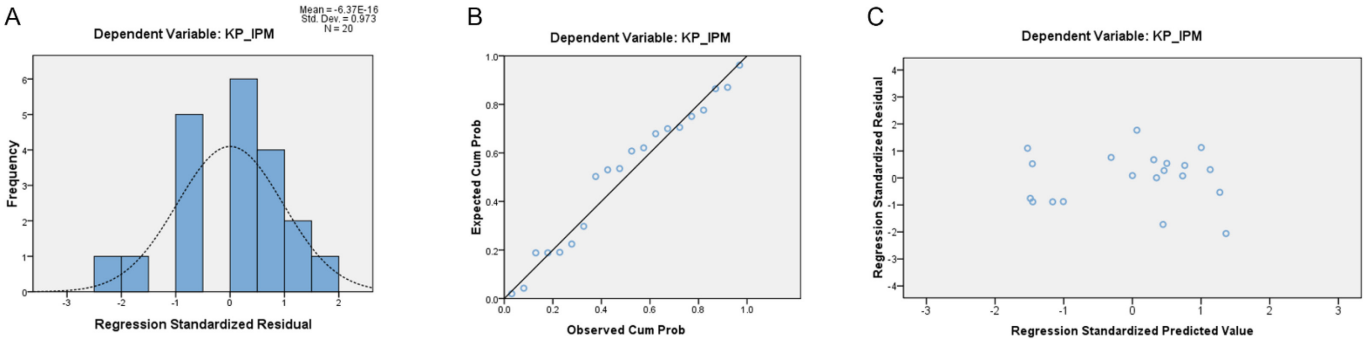
KP: *Klebsiella pneumoniae*; DDD: defined daily dose; IPM: imipenem; TZP: piperacillin/tazobactam; CAZ: ceftazidime; FEP: cefepime; CFS: cefoperazone/sulbactam; ETP: ertapenem; CRO: ceftriaxone; TGC: tigecycline; LVX: levofloxacin; MEM: meropenem.

correlated with only one antibiotic, as detailed in Table 4.

Multiple linear regression analysis

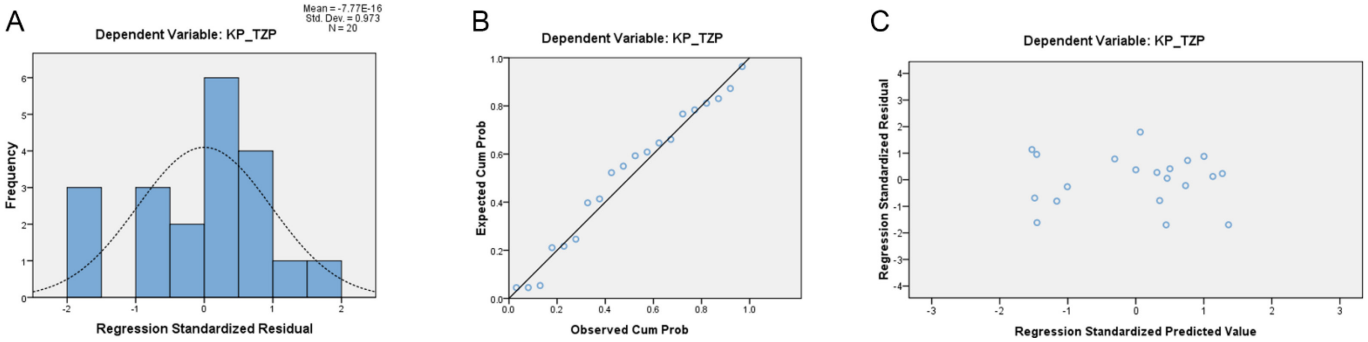
Multiple linear regression was used to further determine whether there were independent, linear, and sig nificant factors in the above correlations. Models 1–3 included multiple variables, while models 4–9 incorporated single variables. Table 5 summarizes the key parameters and test values for each regression model. Figures 1–3 present the diagnostic plots for models 1–3. The results showed that the resistance rates of *K. pneumoniae* to imipenem, piperacillin-tazobactam, and ceftazidime were independently linear, correlated only with piperacillin-tazobactam DDDs, with regression coefficients (β) of 0.221, 0.224, and

Figure 1. Regression diagnostic plots for model 1.



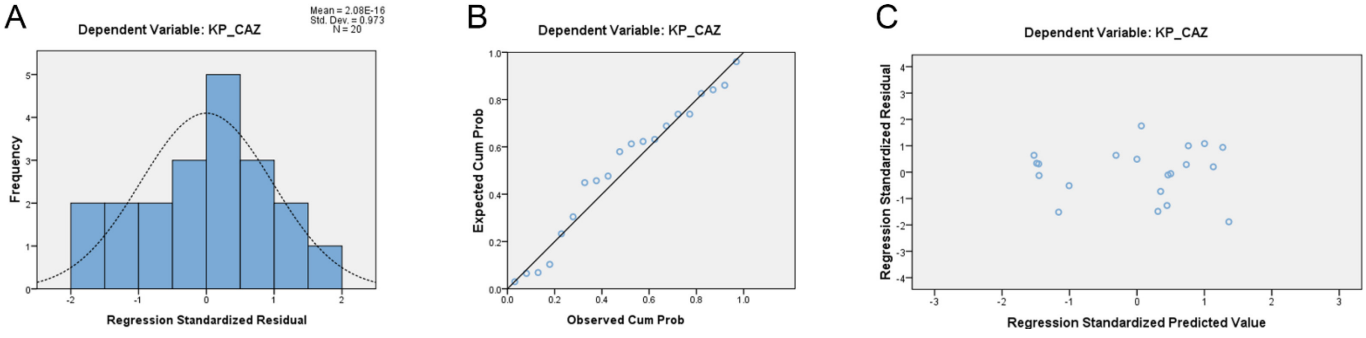
A. Histogram of standardized residuals (normality assessment); B. Normal Q-Q plot (residual normality verification); C. Scatterplot of residuals versus fitted values (homoscedasticity assessment).

Figure 2. Regression diagnostic plots for model 2.



A. Histogram of standardized residuals (normality assessment); B. Normal Q-Q plot (residual normality verification); C. Scatterplot of residuals versus fitted values (homoscedasticity assessment).

Figure 3. Regression diagnostic plots for model 3.



A. Histogram of standardized residuals (normality assessment); B. Normal Q-Q plot (residual normality verification); C. Scatterplot of residuals versus fitted values (homoscedasticity assessment).

0.166, respectively. Moreover, the resistance rates to ceftriaxone, cefoperazone-sulbactam, and ertapenem were also positively correlated with piperacillin-tazobactam DDDs. Resistance to cefepime was positively correlated with ceftazidime DDDs. Resistance to tigecycline was positively correlated with meropenem DDDs. Resistance to levofloxacin was negatively correlated with cefoperazone-sulbactam DDDs.

Discussion

ICU mortality and antimicrobial resistance are elevated owing to comorbidities, invasive procedures, and broad-spectrum antibiotic use [12]; with infection rates substantially greater than in non-ICU settings [13]. *K. pneumoniae* has become the predominant carbapenem-resistant Enterobacteriaceae (CRE) isolate in ICUs [14], leading to extended hospital stays, clinical worsening, and substantial financial implications. This highlights its status as a paramount public health priority [15]. ICU admission, prolonged hospitalization, carbapenem antibiotic use, and invasive procedures have been identified as risk factors; all commonly observed in critically ill ICU populations [16].

In this five-year study, 4,577 bacterial isolates were obtained from ICU specimens, with *K. pneumoniae* representing 20.45% (936/4,577) of cultured organisms. Notably, ICU-derived isolates constituted 34.24% (936/2,734) of total hospital *K. pneumoniae* specimens, demonstrating an increasing prevalence consistent with contemporary research [17]. Respiratory tract infections were most common (66.24%, 620/936 cases), followed by urinary (12.18%) and bloodstream infections (5.66%), aligning with prior studies [18,19] and highlighting the need for stricter respiratory infection control in critical care.

The resistance rate of *K. pneumoniae* isolated from ICU from 2020 to 2024 was generally high, with resistance rates to most antibiotics exceeding 65%, indicating a dire situation of drug-resistance. *K. pneumoniae* in the ICU showed sensitivity to tigecycline, with a resistance rate below 5%. As reported, no species of *Escherichia coli*, *K. pneumoniae*, or *Enterobacter cloacae* were found to be resistant to tigecycline and polymyxin B [20]. Carbapenem-resistant *K. pneumoniae* (CRKP) often shows multidrug resistance, making treatment challenging for infected patients and potentially causing death [21]. The primary therapeutic options for CRKP comprise tigecycline and polymyxin, frequently administered in combination with other antibiotics regimens to potentiate antimicrobial activity and enhance clinical outcomes [22]. Tigecycline demonstrates in vitro susceptibility against CRKP when combined with trimethoprim-sulfamethoxazole, showing partial synergistic effects. This combination presents a potential treatment option for CRKP infections [23]. *K. pneumoniae* in the ICU is highly resistant (> 70%) to quinolones and enzyme inhibitor combinations, rendering them unsuitable, as supported by recent research [24]. The ICU pneumonia-causing *K. pneumoniae* in this study showed similar susceptibility to ceftriaxone, cefoperazone-sulbactam, and tigecycline when compared with data from China Antimicrobial Resistance Surveillance and Research (CARST) 2021–2022 [25]. The resistance rates to piperacillin-tazobactam, cefepime, imipenem, ertapenem, amikacin, and levofloxacin exceed national averages, while trimethoprim-sulfamethoxazole resistance is lower. Studies indicate that the worsening clinical drug resistance of *K. pneumoniae* may be due to the horizontal spread of antimicrobial resistance genes [26]. Significant resistance increases have occurred over the 5 years for piperacillin-tazobactam, cefoperazone-sulbactam, ertapenem, and imipenem; underscoring the need for enhanced antimicrobial stewardship in ICUs.

Bacterial resistance is significantly influenced by microbial characteristics, drug classes, and exposure levels. Pearson analysis showed that the imipenem resistance rate of *K. pneumoniae* in ICU correlated with piperacillin-tazobactam and imipenem DDDs. Multiple linear regression revealed a significant independent linear association between piperacillin-tazobactam DDDs and imipenem resistance ($\beta = 0.221$, 95% CI 0.132–0.309). Model validation confirmed statistical significance ($F = 27.460$, $p < 0.001$), no multicollinearity (variance inflation factor, VIF < 5), and normally distribute, homoscedastic residuals (Figure 1A–1C). An R^2 of 0.604 indicated that piperacillin-tazobactam utilization accounted for 60.4% of the variability in resistance, with the residual variance likely reflecting unmeasured genetic or environmental factors. Imipenem DDDs were excluded from the final model due to insufficient predictive contribution ($p = 0.085$). Mechanistically, it has been shown that rising piperacillin-tazobactam usage drove imipenem resistance in *Pseudomonas aeruginosa*, likely via integron-mediated cross-strain transmission, downregulated outer membrane proteins, and enhanced efflux pump activity [27]. Whether analogous mechanisms underlie *K. pneumoniae* resistance warrants further investigation.

In addition, the multiple linear regression results show that the resistance rate of *K. pneumoniae* in ICU to piperacillin-tazobactam is independently and positively correlated only with its DDDs (β = 0.224, 95% CI 0.129–0.319), a finding consistent with the reports by Chen Jiebing *et al.* [28]. Notably, piperacillin-tazobactam DDDs showed significant independent associations with resistance to ceftazidime, ceftriaxone, cefoperazone-sulbactam, and ertapenem, suggesting that clinical overuse of piperacillin-tazobactam may contribute to multidrug resistance. Moreover, resistance to levofloxacin negatively correlated with cefoperazone-sulbactam DDDs, matching the findings of Liang *et al.* [29]. While contemporary research has confirmed an association between fluoroquinolone resistance and the OqxAB efflux pump [30], whether cefoperazone-sulbactam influences levofloxacin resistance through the efflux system remains to be investigated. Furthermore, resistance to cefepime was positively correlated with ceftazidime DDDs, and resistance to tigecycline was positively correlated with meropenem DDDs. Research has evidenced that bacterial cross- and co-resistance to antimicrobial agents may develop through shared resistance mechanisms, including efflux pump overexpression, altered membrane permeability, enzymatic inactivation, and target modification [31]. The drug resistance rate of *K. pneumoniae* in ICU is linked to antimicrobial DDDs. Rational use of antimicrobials is key to curbing bacterial resistance.

K. pneumoniae resists antibiotics via β-lactamases production, reduced membrane permeability, efflux pumps, target mutations, and metabolic adaptation. These combined mechanisms drive multidrug resistance [17,32]. Research has found that OXA-232-producing CRKP persistently contaminates ICU environments, causing patient colonization and infections [33]. CRKP resistance remains predominantly KPC-mediated among the strains isolated in China [34], while emerging carbapenem-resistant HvKP escalates clinical risks [35].

The ICU is a high-incidence area for hospital infections, with *K. pneumoniae* infections and drug resistance being particularly prominent, posing significant challenges to the treatment of critically ill patients. Specialist clinical units necessitate tailored analyses. Additionally, bacterial resistance mechanisms are complex, and simple one-to-one antibiotic usage-resistance analyses may overlook cross-drug effects. This study used one-to-many correlation analysis to assess ICU *K. pneumoniae* resistance against antibiotic DDDs. Multiple linear regression identified independent predictors, providing novel insights to optimize antimicrobial stewardship.

Rapid clinical deterioration in ICU patients requires prompt antimicrobial therapy to enhance survival and limit healthcare-associated infections. Combating *K. pneumoniae* resistance necessitates urgent multidisciplinary approaches, with antimicrobial stewardship as a priority. The key infection control strategies include minimizing invasive interventions, implementing active surveillance, enforcing strict isolation, and enhancing environmental decontamination to curb resistant strain transmission [36].

Conclusions

The resistance rate of *K. pneumoniae* in the ICU is closely linked to antibiotic use. Hospitals should strengthen resistance monitoring and promote rational use of antibiotics to delay the emergence of resistant species.

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Conflict of interest

No conflict of interest is declared.

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