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Antimicrobial resistance and risk factors for mortality of pneumonia caused by *Klebsiella pneumoniae* among diabetics: a retrospective study conducted in Shanghai, China

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Purpose: To investigate antimicrobial resistance and risk factors for mortality of *Klebsiella pneumoniae* (KP) pneumonia in diabetics and nondiabetics.

Patients and methods: A retrospective study was conducted among inpatients of KP pneumonia via electronic medical records in a territory hospital between January 2016 and June 2018. Antimicrobial resistance in KP pneumonia was compared between diabetics and nondiabetics. Independent risk factors for mortality in KP pneumonia were identified by univariate and multivariate logistic regression among diabetics and nondiabetics separately.

Results: In this study, 456 patients with KP pneumonia were included. There were 156 cases with diabetes and 300 without diabetes. KP showed a lower antimicrobial resistance to a multitude of antimicrobials in pneumonia among diabetics than nondiabetics, namely aztreonam, cefotetan, sulperazone, meropenem, amikacin, tobramycin, sulfamethoxazole, and fosfomycin. In addition, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) was more prevalent among nondiabetics than diabetics who were admitted to intensive care unit (ICU) (63.0% vs 45.1%, $P = 0.038$). Multivariable analysis showed that independent risk factors for in-hospital mortality (IHM) in KP pneumonia among diabetics differed from that among nondiabetics as well. Independent predictors for IHM of KP pneumonia among diabetics were male (OR: 5.89, 95% CI: 1.34–25.93, $P = 0.019$), albumin (ALB) < 35 g/L (OR: 7.00, 95% CI: 2.02–24.28, $P = 0.002$), bloodstream infection (BSI) (OR: 21.14, 95% CI: 3.18–140.72, $P = 0.002$), and invasive ventilation during hospitalization (OR: 8.00, 95% CI: 2.99–21.42, $P < 0.001$). In nondiabetics, independent predictors were higher CURB-65 score (OR: 1.92, 95% CI: 1.29–2.86, $P = 0.001$), CRKP (OR: 2.72, 95% CI: 1.07–6.90, $P = 0.035$), BSI (OR: 4.98, 95% CI: 1.34–18.50, $P = 0.017$), and ICU admission (OR: 4.06, 95% CI: 1.57–10.47, $P = 0.004$).

Conclusion: In KP pneumonia, diabetics showed lower antimicrobial resistance and different independent risk factors for mortality compared with nondiabetics, in line with previous studies. Importantly, further attention should be paid on rational and effective antibiotic and supportive treatments in order to reduce mortality without aggravating antimicrobial resistance and metabolic damage among diabetics.

Keywords: *Klebsiella pneumoniae*, pneumonia, diabetics, antimicrobial resistance, risk factor, mortality

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Introduction

Pneumonia is a leading cause of death in infectious diseases according to the report released by the World Health Organization (WHO).[1] In addition, it was reported by China Antimicrobial Surveillance Network (CHINET) that *Klebsiella pneumoniae (KP)* ranked as the most frequently isolated pathogen in respiratory tract.[2] KP is a scary gram-negative bacterium with high lethality owing to constantly emerging traits of either multi-resistance or hypervirulence.[3] As an opportunistic pathogen, it is more likely to cause infections in individuals with impaired immune functions.[3] Diabetes, with a global prevalence of 425 million in 2017 and 629 million predicted in 2045,[4] are definitely one of the largest immunocompromised groups.[5] Moreover, elevated glucose concentration of airway surface liquid (ASL) can provide abundant nutrients for bacteria, complicating the clinical picture of KP pneumonia in diabetics.[6]

However, information regarding the antimicrobial resistance of KP in pneumonia or other infections is limited and varied.[7–12] To our knowledge, only one study has explored the difference in the risk factors for mortality of pneumonia between diabetics and nondiabetics.[13] Considering the harmful effects of antibiotics on metabolism and the high susceptibility to acquire KP pneumonia in diabetics,[5,14] it is important to have a better understanding of antimicrobial resistance and risk factors for mortality in this risk group. Our study was designed to make a relatively comprehensive exploration on antimicrobial resistance and risk factors for in-hospital mortality (IHM) of KP pneumonia with and without diabetes.

Material and methods

Study design and data collection

A retrospective study was conducted between January 2016 and June 2018 among inpatients of KP pneumonia with and without diabetes in Ruijin Hospital, Shanghai, China. Data were extracted and collected from medical records. We collected information on baseline characteristics, laboratory tests, treatment, procedures, and outcomes. Only the first positive KP culture in sputum or blood sample of each patient was included in our analysis. Readmission was excluded and only the first hospitalization of each patient was herein included. Only patients with antimicrobial tests on imipenem, meropenem, and ertapenem were included in the analysis of carbapenem-resistant *Klebsiella pneumoniae* (CRKP). In addition, patients with automatic discharges were excluded on the analysis of the outcome.

Definitions

Pneumonia was defined according to Centers for Disease Control and Prevention (CDC) (Atlanta, GA, USA).[15] Besides, KP pneumonia was confirmed by KP identification in a sputum culture.

The diagnosis of diabetes was based on (i) history of diabetes or hypoglycemic drug consumption or (ii) symptoms of diabetes and casual blood glucose concentrations ≥11.1 mmol/L or (iii) fasting plasma glucose ≥7 mmol/L or (iv) 2-h plasma glucose in an oral glucose tolerance test (OGTT) ≥11.1 mmol/L.[16]

IHM referred to overall IHM during hospitalization.

Microbiology

KP isolates were identified by Vitek 2 system (bioMérieux, Marcy l'Etoile, France). Antimicrobial susceptibility tests were conducted with disk diffusion method or Vitek 2 system.[17] Extended-spectrum beta-lactamase (ESBL) screening was carried out with the aid of clavulanic acid synergy test.[17] Escherichia coli ATCC 25922 was used as a quality control reference strain. The results were interpreted in accordance with the recommendations of the Clinical and Laboratory Standards Institute (CLSI2018).[17] KP isolates resistant to imipenem, meropenem, or ertapenem was classified as CRKP.[17]

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range). Categorical variables were shown as counts or counts/total (percentages). Statistical comparisons were performed using the Student's *t*-test or Mann–Whitney U-test, chi-square test or fisher's exact test, as appropriate. Risk factors for IHM were explored using univariate and multivariate logistic regression analyses in a Forward stepwise (likelihood ratio) manner, and the results were listed as odds ratios (95% confidence interval). Statistics were analyzed using SPSS 24.0 software (IBM, Armonk, NY, USA). Two-sided significance level of 0.05 was selected.

Results

Sociodemographic and clinical characteristic of KP pneumonia patients with and without diabetes

In this study, 456 patients with KP pneumonia were included. There were 156 cases with diabetes and 300 without diabetes (Table 1). Diabetics, compared with nondiabetics, were older

Table 1 Sociodemographic and clinical characteristic of KP pneumonia patients with and without diabetes

	Diabetics (n = 156)	Nondiabetics (n = 300)	*P*-value
Age	66.5±13.8	62.7±16.5	**0.030**
Male	115(73.7)	214(71.3)	0.590
BMI	24.2±4.3	22.9±4.2	**0.002**
Current smoking status	47 (30.1)	79 (26.3)	0.390
Hospitalization within 3 months	36(23.1)	88(29.3)	0.610
Antimicrobial exposure within 3 months	53 (34.0)	118 (39.3)	0.262
Carbapenems	16(10.3)	38(12.7)	0.450
Other β-lactams	34(21.8)	79(26.3)	0.287
Aminoglycosides	26(16.7)	50(16.7)	1.000
Quinolones	21(13.5)	44(14.7)	0.727
Polypeptides	8(5.1)	17(5.7)	0.811
Catheter at admission			
Tracheal intubation and tracheostomy	17(10.9)	33(11.0)	0.973
CVC	13(8.3)	32(10.7)	0.428
Comorbidities			
Chronic lung diseases	31(19.9)	62(20.7)	0.842
Chronic heart diseases	67(42.9)	72(24.0)	**< 0.001**
Chronic renal diseases	20(12.8)	20(6.7)	**0.028**
Stroke	39(25.0)	45(15.0)	**0.009**
Hypertension	97(62.2)	117(39.0)	**< 0.001**
Cirrhosis	11(7.1)	19(6.3)	0.769
Current malignancy	13(8.3)	21(7.0)	0.607
FBG (mmol/L)	9.7±4.6	6.1±2.3	**< 0.001**
$HbA1_C$ (%)	8.6±3.2	5.7±0.6	**< 0.001**
HAP	112(71.8)	210(70.0)	0.690
Poly-microbial pneumonia	44(28.2)	101(33.7)	0.235
Antimicrobial consumption at hospitalization			
Cephalosporin	99 (63.5)	201 (67.0)	0.450
Carbapenems	68(43.6)	128(42.7)	0.850
β-lactam combination agents	41(26.3)	76(25.3)	0.826
Fosfomycin	6 (3.8)	18 (6.0)	0.328
Tigecycline	23(14.7)	34(11.3)	0.296
Invasive ventilation at hospitalization	51(32.7)	80(27.1)	0.164
CURB-65 score	1.7±0.1	1.4±0.1	**0.013**
KP BSI	16 (10.3)	22 (7.3)	0.284
ICU admission	75(48.1)	111(37.0)	**0.022**
LOS	27.0(16.0–47.3)	26.5(15.0–49.0)	0.848

Notes: Significant *p*-values (< 0.05) were presented in bold.
Abbreviations: ALB, albumin; BMI, body mass index; BSI, bloodstream infection; CVC, central venous catheter; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HAP, hospital-acquired pneumonia; ICU, intensive care unit; KP, *Klebsiella pneumoniae*; LOS, length of stay.

(66.5 vs 62.7 years), together with a higher body mass index (BMI) (24.2 vs 22.9) and more coexisting diseases such as chronic heart diseases (42.9% vs 24.0%), chronic renal diseases (12.8% vs 6.7%), stroke (25.0% vs 15.0%), and hypertension (62.2% vs 39.0%). Moreover, diabetics suffered from much severe KP pneumonia with a higher intensive care unit (ICU) admission rate (48.1% vs 37.0%) and CURB-65 score (1.7 vs 1.4).

Antimicrobial resistance of KP in sputum among diabetics and nondiabetics

All the 456 patients had a positive KP culture in sputum. In 38 (8.3%) patients, KP was also isolated from blood (Table 2). ESBLs tests were conducted in 417 (91.4%) patients. Besides, 357 (78.3%) patients experienced antimicrobial tests on imipenem, meropenem, and ertapenem. The level of HbA1c was available in 83 (53.2%) diabetics.

Table 2 Antimicrobial resistance rate of *Klebsiella pneumoniae* cultured from sputum in pneumonia patients with and without diabetes

	No. of resistance, CRKP or ESBL-KP/total no. of tested (%)											
	Overall population (n = 456)			ICU (n = 186)			Non-ICU (n = 270)			Diabetics with HbA1C (n = 83)		
	Diabetics	Nondiabetics	*P*-value	Diabetics	Nondiabetics	*P*-value	Diabetics	Nondiabetics	*P*-value	HbA1c≥6.5%	HbA1c < 6.5%	*P*-value
Ampicillin	146/153 (95.4)	269/285 (94.4)	0.642	72/74 (97.3)	103/105 (98.1)	0.722	74/79 (93.7)	166/180 (92.2)	0.681	66/70 (94.3)	11/13 (84.6)	0.236
Cefazolin	85/150 (56.7)	160/281 (56.9)	0.957	54/72 (75.0)	85/106 (80.2)	0.411	31/78 (39.7)	75/175 (42.9)	0.643	34/68 (50.0)	8/13 (61.5)	0.446
Ceftazidime	57/154 (37.8)	109/285 (38.2)	0.799	40/74 (54.1)	70/105 (66.7)	0.088	17/80 (21.3)	39/180 (21.7)	0.940	22/70 (31.4)	4/13 (30.8)	1.000
Ceftriaxone	71/152 (46.7)	137/282 (48.6)	0.710	46/73 (63.0)	79/106 (74.5)	0.099	25/79 (31.6)	58/176 (33.0)	0.837	29/69 (42.0)	6/13 (46.2)	0.785
Cefepime	48/154 (31.2)	92/286 (32.2)	0.830	37/74 (50.0)	63/106 (59.4)	0.210	11/80 (13.8)	29/180 (16.1)	0.626	17/70 (24.3)	4/13 (30.8)	0.730
Aztreonam [b]	59/151 (39.1)	123/281 (43.8)	0.346	39/73 (53.4)	73/105 (69.5)	**0.029**	20/78 (25.6)	50/176 (28.4)	0.649	21/68 (30.9)	5/13 (38.5)	0.747
Cefotetan [b]	47/151 (31.1)	100/282 (35.5)	0.494	33/73 (45.2)	67/106 (63.2)	**0.017**	14/78 (17.9)	33/176 (18.8)	0.879	16/69 (23.2)	5/13 (38.5)	0.302
Unasyn	61/153 (39.9)	120/284 (42.3)	0.629	43/73 (58.9)	75/106 (70.8)	0.100	18/80 (22.5)	45/178 (25.3)	0.631	24/70 (34.3)	4/13 (30.8)	1.000
Sulperazone [d]	34/130 (26.2)	81/271 (29.9)	0.573	26/62 (41.9)	56/102 (54.9)	0.107	8/68 (11.8)	25/169 (14.8)	0.542	7/60 (11.7)	4/10 (40.0)	**0.044**
PTZ	43/154 (27.9)	84/284 (29.6)	0.715	33/74 (44.6)	61/105 (58.1)	0.075	10/80 (12.5)	23/179 (12.8)	0.938	13/70 (18.6)	4/13 (30.8)	0.453
Imipenem	48/154 (31.2)	92/286 (32.2)	0.830	36/74 (48.6)	63/106 (59.4)	0.152	12/80 (15.0)	29/180 (16.1)	0.821	15/70 (21.4)	4/13 (30.8)	0.482
Meropenem [b]	30/119 (25.2)	77/248 (31.0)	0.249	20/53 (37.7)	55/92 (59.8)	**0.011**	10/66 (15.2)	22/156 (14.1)	0.839	8/57 (14.0)	3/9 (33.3)	0.165
Ertapenem	49/149 (32.9)	101/280 (36.1)	0.510	35/72 (48.6)	67/106 (63.2)	0.053	14/77 (18.2)	34/174 (19.5)	0.801	16/67 (23.9)	5/13 (38.5)	0.310
Ciprofloxacin	58/154 (37.7)	104/285 (36.5)	0.808	41/74 (55.4)	66/62.3 (62.3)	0.356	17/80 (21.3)	38/179 (21.2)	0.997	22/70 (31.4)	4/13 (30.8)	1.000
Levofloxacin	48/151 (31.8)	97/282 (34.4)	0.584	37/73 (50.7)	61/106 (57.5)	0.365	11/78 (14.1)	36/176 (20.5)	0.229	15/69 (21.7)	4/13 (30.8)	0.486
Amikacin [b]	38/154 (24.7)	80/286 (28.0)	0.457	28/74 (37.8)	56/106 (52.8)	**0.047**	10/80 (12.5)	24/180 (13.3)	0.854	10/70 (14.3)	4/13 (30.8)	0.219
Gentamicin	51/154 (33.1)	111/286 (38.8)	0.368	40/74 (54.1)	69/106 (65.1)	0.136	11/80 (13.8)	42/180 (23.3)	0.077	17/70 (24.3)	4/13 (30.8)	0.730
Tobramycin [b]	43/151 (28.5)	92/278 (33.1)	0.325	31/73 (42.5)	64/105 (61.0)	**0.015**	12/78 (15.4)	28/173 (16.2)	0.873	15/69 (21.7)	4/13 (30.8)	0.486
SMZ[a, c]	35/154 (22.7)	93/286 (32.5)	**0.031**	24/74 (32.4)	47/106 (44.3)	0.108	11/80 (13.8)	46/180 (25.6)	**0.034**	13/70 (18.6)	4/13 (30.8)	0.453
Tigecycline	5/104 (4.8)	10/221 (4.5)	0.910	4/46 (8.7)	8/86 (9.3)	0.908	1/58 (1.7)	2/135 (1.5)	0.938	2/49 (4.1)	0/7 (0)	1.000
Fosfomycin [a,b,d]	31/116 (26.7)	97/258 (37.6)	**0.040**	23/54 (42.6)	62/99 (62.6)	**0.017**	8/62 (12.9)	35/159 (22.0)	0.124	8/56 (14.3)	4/6 (66.7)	**0.011**
Nitrofurantoin	59/147 (40.1)	107/266 (40.2)	0.986	41/70 (58.6)	66/103 (64.1)	0.464	18/77 (23.4)	41/163 (25.2)	0.765	22/65 (33.8)	6/13 (46.2)	0.528
CRKP [b]	37/114 (32.5)	92/243 (37.9)	0.322	23/51 (45.1)	58/92 (63.0)	**0.038**	14/63 (22.2)	34/151 (22.5)	0.962	12/54 (22.2)	4/9 (44.4)	0.156
ESBL-KP	27/147 (18.4)	48/270 (17.8)	0.881	14/73 (19.2)	14/100 (14.0)	0.361	13/74 (17.6)	34/170 (20.4)	0.658	13/67 (19.4)	2/12 (16.7)	1.000

Notes: a: $p < 0.05$ between diabetics and nondiabetics in overall population; b: $p < 0.05$ between diabetics and nondiabetics in the intensive care unit (ICU); c: $p < 0.05$ between diabetics and nondiabetics in the non-intensive care unit (non-ICU); d: $p < 0.05$ between those HbA1c≥6.5% and < 6.5% in diabetics;

Abbreviations: PTZ: piperacillin-tazobactam; SMZ: sulfamethoxazole.

Among 22 drugs commonly used clinically, KP showed lower resistance to sulfamethoxazole (SMZ) (22.7% vs 32.5%) and fosfomycin (26.7% vs 37.6%) in pneumonia among diabetics. In ICU, resistance rates of KP to aztreonam (53.4% vs 69.5%), cefotetan (45.2% vs 63.2%), meropenem (37.7% vs 59.8%), amikacin (37.8% vs 52.8%), tobramycin (42.5% vs 61.0%), and fosfomycin (42.6% vs 62.6%) were significantly lower in diabetics than that in nondiabetics. Besides, diabetics were shown to have a lower prevalence of CRKP (45.1% vs 63.0%). In non-ICU, only SMZ displayed a lower resistance degree (13.8% vs 25.6%). Compared with diabetics with HbA1c < 6.5%, those with a higher HbA1c level showed significantly lower resistance to sulperazone (11.7% vs 40.0%) and fosfomycin (14.3% vs 66.7%). No significant difference in ESBLs distribution was found between diabetics and nondiabetics.

IHM in KP pneumonia and bloodstream infection (BSI) among diabetics and nondiabetics

Here, 43 (9.4%) patients were of auto-discharge and excluded in the analysis of the outcome. IHM of KP pneumonia was higher in diabetics than nondiabetics (25.5% vs 16.4%). No significant difference in IHM was found in ESBL-KP pneumonia, CRKP pneumonia, or CRKP-BSI between diabetics and nondiabetics as well (Table 3).

Risk factors for IHM in KP pneumonia patients with and without diabetes

We conducted univariate and multivariate logistic regression analyses in KP pneumonia patients with and without diabetes, respectively (Tables 4 and 5). In diabetics, risk factors for IHM in KP pneumonia were male (OR: 5.89, 95% CI: 1.34–25.93), ALB < 35 g/L (OR: 7.00, 95% CI: 2.02–24.28), KP-BSI (OR: 21.14, 95% CI: 3.18–140.72), and invasive ventilation during hospitalization (OR: 8.00, 95% CI: 2.99–21.42). In nondiabetics, independent predictors for IHM in KP pneumonia were higher CURB-65 score (OR: 1.92, 95% CI: 1.29–2.86), CRKP (OR: 2.72, 95% CI: 1.07–6.90), KP-BSI (OR: 4.98, 95% CI: 1.34–18.50), and ICU admission (OR: 4.06, 95% CI: 1.57–10.47).

Table 3 In-hospital mortality of *Klebsiella pneumoniae* pneumonia and bloodstream infection with and without diabetes

	No. of death/total no. (%)		
	Diabetics	**Nondiabetics**	***P*-value**
KP pneumonia	37/145(25.5)	44/268(16.4)	**0.026**
ESBL-KP pneumonia	8/24 (33.3)	10/46 (21.7)	0.292
CRKP pneumonia	11/34 (32.4)	25/77 (32.5)	0.991
CRKP BSI	5/7 (71.4)	10/15 (66.7)	1.000

Notes: Significant *p*-values (< 0.05) were presented in bold.
Abbreviations: BSI, bloodstream infection; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; ESBL-KP, extended-spectrum β-lactamase-*Klebsiella pneumoniae*; KP, *Klebsiella pneumoniae*.

Discussion

In this study, a comprehensive exploration on antimicrobial resistance and risk factors for IHM in KP pneumonia patients with and without diabetes was carried out. We found that: (1) Antimicrobial resistance of KP to several commonly used drugs in pneumonia was lower in diabetics than in nondiabetics. Furthermore, in diabetics, antimicrobial resistance was lower in those HbA1c ≥6.5% than that in those HbA1c < 6.5%; (2) Diabetics showed a lower prevalence of CRKP in KP pneumonia among patients admitted to ICU; (3) Independent risk factors for IHM in diabetics and nondiabetics were different: male, ALB < 35 g/L, KP-BSI, and invasive ventilation during hospitalization in diabetics, compared with higher CURB-65 score, CRKP, KP-BSI, and ICU admission in nondiabetics.

Diabetics had higher BMI and more commodities, and were more advanced in age compared with nondiabetics, which was also found in previous studies.[13,18] Additionally, pneumonia in diabetics were shown to be of higher severity in our study and previous studies.[9,13,18]

The overall antimicrobial resistance rate in our study was higher than that presented in a report published by CHINET,[2] showing the severe condition of drug resistance, particularly in tertiary hospitals.[11] Out of our expectation, we found that diabetics were of lower resistance to antimicrobials than nondiabetics. It was reported that glucose could stimulate the uptake of aminoglycoside antimicrobials by promoting the TCA cycle and thus restore the susceptibility of bacteria, including KP.[19] However, a slight similar effect was found regarding β-lactams and quinolones.[19] According to a study, KP possessed orthologs of mammalian 3-mercaptopyruvate sulfurtransferase (3MST), which could provide resistance to a multitude of antimicrobials by catalyzing the production of hydrogen sulfide (H_2S).[20] Furthermore, hyperglycemia and diabetes were demonstrated to impair the 3-MP/3-MST/H_2S pathway, leading to a decreased level of H_2S.[21] We found a higher prevalence of CRKP in pneumonia

Table 4 Univariate and multivariate analyses of independent predictors for in-hospital mortality in *Klebsiella pneumoniae* pneumonia among diabetics

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	***P*-value**	**Odds ratio (95% CI)**	***P*-value**
Male	3.47(1.14–10.61)	**0.029**	5.89(1.34–25.93)	**0.019**
Age ≥65	2.24(0.99–5.08)	0.053		
BMI	0.96(0.88–1.05)	0.396		
Chronic lung diseases	1.51(0.61–3.70)	0.373		
Hypertension	2.69(1.13–6.42)	**0.026**		
Chronic heart diseases	2.23(1.05–4.77)	**0.038**		
Stroke	1.17(0.50–2.73)	0.720		
Chronic renal diseases	5.29(1.93–14.49)	**0.001**		
FBG	0.99(0.89–1.09)	0.759		
HbA1c	1.07(0.93–1.24)	0.336		
CURB-65 score	1.64(1.20–2.24)	**0.002**		
ALB < 35 g/L	7.24(2.40–21.85)	**< 0.001**	7.00(2.02–24.28)	**0.002**
Surgery	1.63(0.76–3.48)	0.206		
HAP	2.06(0.82–5.14)	0.123		
CRKP	2.08(0.83–5.25)	0.119		
ESBL-KP	1.52(0.59–3.93)	0.389		
Poly-microbial pneumonia	2.43(1.12–5.28)	**0.025**		
KP-BSI	17.04(3.48–83.35)	**< 0.001**	21.14(3.18–140.72)	**0.002**
Invasive ventilation at hospitalization	7.70(3.36–17.63)	**< 0.001**	8.00(2.99–21.42)	**< 0.001**
ICU admission	8.22(3.30–20.51)	**< 0.001**		

Notes: Significant *p*-values (< 0.05) were presented in bold.
Abbreviations: ALB, albumin; BMI, body mass index; BSI, bloodstream infection; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; ESBL-KP, extended-spectrum β-lactamase-*Klebsiella pneumoniae*; FBG, fasting blood glucose; HAP. hospital-acquired pneumonia; HbA1c, hemoglobin A1c; ICU, intensive care unit; KP: *Klebsiella pneumoniae*.

among diabetics admitted to ICU, in accordance with a previous study on CRKP-BSI.[7] A previous study has shown that diabetes was an independent risk factor for hypervirulent (hypermucoviscous) KP (HvKP or HMKP) infection.[22] In another study, it has been reported that high glucose levels could stimulate biosynthesis of capsular polysaccharide (CPS), and that could be helpful in evading phagocytosis, as well as killing, leading to increase of invasiveness and virulence.[23] Hypervirulent and multi-drug-resistant KP were generally separated and HvKP often presented a low antimicrobial resistance.[22,24] However, it was shown in a previous study that KP possessed a higher resistance to some commonly used drugs in liver abscess.[9] Since no statistic on previous antibiotics exposure of patients was present in the former study, we could not figure out whether diabetics and nondiabetics had a comparably previous antibiotics use, which could act as a force of natural selection.[9] In another study on urinary tract infection in women, antimicrobial resistances of KP and other uropathogens to first-line treatment antibiotics were comparable in Type 2 diabetics and nondiabetics.[25] Only 53 KP isolates were included in the analysis of resistance, which is a relatively small sample size.[25] No association was found between ESBL-KP pneumonia and diabetes, in line with a previous study on KP-BSI.[10]

Although HvKP and CRKP were usually separated,[22,24] hypervirulent CRKP and carbapenem-resistant HvKP have occurred by the acquisition of virulent or resistant plasmid, which was easy to transfer among bacteria.[24,26] Even worse, it was reported that the use of antimicrobials might be detrimental to metabolism, elevating the risk of development of diabetes.[14] Therefore, there could be a tendency that diabetics may become the target of super bacteria with combination of hypervirulence and multi-resistance in the future. As a result, the prospect of the war against KP would be much tougher in diabetics. Although the drug resistance rate in diabetics observed in our study was obviously low, the application of antimicrobials in the treatment of KP pneumonia was similar. Further attention should be paid to the appropriate use of antimicrobials in diabetes clinically.

A guideline in China reported that the mean all-cause mortality in hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) was 22.3% and

Table 5 Univariate and multivariate analyses of independent predictors for in-hospital mortality in *Klebsiella pneumoniae* pneumonia among nondiabetics

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	***P*-value**	**Odds ratio (95% CI)**	***P*-value**
Male	0.90(0.45–1.80)	0.755		
Age ≥65	2.39(1.19–4.80)	**0.015**		
BMI	0.95(0.88–1.03)	0.178		
Chronic lung diseases	2.31(1.13–4.69)	**0.021**		
Hypertension	1.52(0.79–2.90)	0.208		
Chronic heart diseases	2.00(0.99–4.04)	0.053		
Stroke	2.82(1.32–6.01)	**0.007**		
Chronic renal diseases	3.66(1.33–10.06)	**0.012**		
FBG	1.00(0.82–1.21)	0.984		
HbA1c	2.18(0.81–5.85)	0.122		
CURB-65 score	2.40(1.76–3.27)	**< 0.001**	1.92(1.29–2.86)	**0.001**
ALB < 35 g/L	3.21(1.37–7.52)	**0.007**		
Surgery	0.65(0.33–1.29)	0.217		
CRKP	6.30(2.83–14.03)	**< 0.001**	2.72(1.07–6.90)	**0.035**
HAP	0.58(0.30–1.13)	0.107		
ESBL-KP	1.48(0.67–3.29)	0.337		
Poly-microbial pneumonia	0.99(0.51–1.94)	0.976		
KP-BSI	9.12(3.25–25.57)	**< 0.001**	4.98(1.34–18.50)	**0.017**
Invasive ventilation at hospitalization	5.54(2.80–10.97)	**< 0.001**		
ICU admission	7.46(3.61–15.43)	**< 0.001**	4.06(1.57–10.47)	**0.004**

Notes: Significant *p*-values (< 0.05) were presented in bold.
Abbreviations: ALB, albumin; BMI, body mass index; BSI, bloodstream infection; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; ESBL-KP, extended-spectrum β-lactamase-*Klebsiella pneumoniae*; FBG, fasting blood glucose; HAP, hospital-acquired pneumonia; HbA1c, hemoglobin A1c; ICU, intensive care unit; KP, *Klebsiella pneumoniae*.

34.5%, respectively.[27] However, the IHM of KP pneumonia in our study was relatively low, which might be explained by a difference in pathogens and the exclusion of auto-discharge in the analysis of outcome. And, patients with auto-discharge were likely to end-up with bad outcome. Tian et al reported a 28-day mortality of 33.3% in CRKP-BSI.[7] A previous study, which considered discharge to hospice as death, reported an IHM of 39% both in CRKP pneumonia and CRKP-BSI.[28] In this study, IHM in CRKP pneumonia was similar with the previous study but mortality in CRKP-BSI was much higher,[7,28] which could be justified by the fact that CRKP-BSI in our study was mainly developed from lung infections, which was more likely to die.[7]

Both fasting blood glucose (FBG) and HbA1c levels, regardless of diabetic conditions, did not seem to influence the outcome in our study. It might be related to the fact that hospital glycemia was often influenced by not only diabetic conditions but also stress status.[29] It was suggested that chronic hyperglycemia and severe acute hyperglycemia might be detrimental, but mild to moderate stress hyperglycemia was protective.[30] However, it remained unclear at what threshold stress hyperglycemia became detrimental.[30] HbA1c was only obtained from 149 patients, so the sample size might be insufficient to estimate the long-term blood glucose control levels. As a result, the impact of FBG and HbA1c levels on mortality in KP pneumonia needs to be further studied.

BSI was identified as a powerful risk factor for mortality both in diabetics and nondiabetics, which was in line with previous studies.[18] The effect of gender on mortality for patients with infectious diseases in diabetics and nondiabetics was controversial.[13,18,31] In our study, males showed to be an independent risk factor for IHM in diabetics alone. It was reported that X chromosome carries several genes involved in innate and adaptive immunity, and sex hormones play an important role in modulating immune molecules.[32] Consequently, females possessed less susceptibility and mortality to various infections, and the double immunosuppressive effect from gene and hyperglycemia may determine higher risk of death in male diabetics.[33] KP pneumonia among diabetics with ALB<35 g/L was poor, which is consistent with previous studies in community-acquired KP-BSI with type 2 diabetes.[34] Compared with nondiabetics, diabetics are of elevated glycation, glycoxidation, and excretion,

and decreased synthesis of ALB.[35] Glycated albumin (GA) and HbA1c could in turn exacerbate the existent deleterious effects of diabetes on ALB.[35] And, decreased ALB level in plasma or serum serves as a risk factor for development of complications.[35] As a result, diabetic patients might suffer much more than nondiabetics owing to ALB deficiency. In a previous study, mechanical ventilation was shown to be an independent predictor for IHM of KP infections.[36] Invasive mechanical ventilation was selected as an independent risk factor in diabetics, but not in nondiabetics in our analysis. This is probably due to the fact that diabetics had more diffusion impairment in lung function, as well as difficulties on wound healing caused by the invasive manipulation. Furthermore, CURB-65 score and ICU admission are two important indicators of severity in pneumonia. In our study, both of them were independent predictors of IHM in KP pneumonia among nondiabetics, but not among diabetics. Diabetics tended to be older, with more kidney and cardiovascular impairment. As a result, diabetics might be affected by a similar higher severity when they suffer from KP pneumonia, and less difference in severity might lead to less negative influences on IHM compared with other risk factors or nondiabetics. Ben-David et al indicated that CRKP was independently associated with increased mortality in BSI.[36] In the present study, CRKP was found to be independently associated with increased mortality in nondiabetics. As mentioned above, hyperglycemia could reduce or reverse drug resistance to some extent, and thus alleviate the harmful impact of drug-resistant bacteria.[19–21]

There are certain limitations in the present study. First, this was a retrospective study and data were retrieved from previous electronic medical records. Therefore, some information, including some antimicrobial susceptibility results, was incomplete. Second, patients with potential KP pneumonia but without a positive sputum culture were not included in our study. Third, there might have been certain misclassification of infection and colonization to some degrees, as patients who suffer from major operations or heart failure might also have pulmonary infiltration. Fourth, our findings in antimicrobial resistance and its mechanism need further validation in metabolomics, genomics, and a larger population, which is also the emphases of our future study.

At the same time, we contrast the antimicrobial resistance of pneumonia-causing KP, which is a hot topic recently, in different subgroups to make the results more reliable. Moreover, we made an exploration on difference on risk factors for IHM between diabetics and nondiabetics, which was a relatively poor investigated approach.

Conclusion

In conclusion, we demonstrated that KP was associated with lower antimicrobial resistance in pneumonia among diabetics clinically. In addition, prevalence of CRKP in KP pneumonia was lower among diabetics who stayed in ICU than nondiabetics. Independent risk factors for IHM of KP pneumonia in diabetics and nondiabetics were not the same. Importantly, further attention should be paid on rational and effective antibiotic and supportive treatments in order to reduce mortality without aggravating antimicrobial resistance and metabolic damage.

Ethics approval and informed consent

The Ethics Committee of Ruijin Hospital gave approval for this study, and all patients provided written informed consent, in compliance with the Declaration of Helsinki.

Abbreviation list

ALB, albumin; BMI, body mass index; BSI, bloodstream infection; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CVC, central venous catheter; ESBL, extended-spectrum β-lactamase; ESBL-KP, extended-spectrum β-lactamase-*Klebsiella pneumoniae*; FBG, fasting blood glucose; HAP, hospital-acquired pneumonia; HbA1c, hemoglobin A1c; ICU, intensive care unit; KP, *Klebsiella pneumoniae*; LOS, length of stay; PTZ, piperacillin-tazobactam; SMZ, sulfamethoxazole.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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