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ORIGINAL ARTICLE

Retrospective Cohort Study

Klebsiella pneumoniae infections after liver transplantation: Drug resistance and distribution of pathogens, risk factors, and influence on outcomes

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Abstract

BACKGROUND

Liver transplantation (LT) is the only curative treatment for end-stage liver disease. However, LT recipients are susceptible to infection, which is the leading cause of early mortality after LT. *Klebsiella pneumoniae* infections (KPIs) in the bloodstream are common in LT recipients. We hypothesized that KPIs and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections may affect the outcomes of LT recipients.

AIM

To assess KPI incidence, timing, distribution, drug resistance, and risk factors following LT and its association with outcomes.

METHODS
This retrospective study included 406 patients undergoing LT at The Third Xiangya Hospital of Central South University, a tertiary hospital, from January 2015 to January 2023. We investigated the risk factors for KPIs and assessed the impact of KPIs and CRKP infections on the prognosis of LT recipients using logistic regression analysis.

RESULTS
KPI incidence was 7.9% (n = 32), with lung/thoracic cavity the most frequent site of infection; the median time from LT to KPI onset was 7.5 d. Of 44 *Klebsiella pneumoniae* isolates, 43 (97.7%) and 34 (77.3%) were susceptible to polymyxin B or ceftazidime/avibactam and tigecycline, respectively; > 70% were resistant to piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, and levofloxacin. Female sex [odds ratio (OR) = 2.827, 95% confidence interval (CI): 1.256-6.364; P = 0.012], pre-LT diabetes (OR = 2.794, 95%CI: 1.070-7.294; P = 0.036), day 1 post-LT alanine aminotransferase (ALT) levels ≥ 1500 U/L (OR = 3.645, 95%CI: 1.671-7.950; P = 0.001), and post-LT urethral catheter duration over 4 d (OR = 2.266, 95%CI: 1.016-5.054; P = 0.046) were risk factors for KPI. CRKP infections, but not KPIs, were risk factors for 6-month all-cause mortality post-LT.

CONCLUSION
KPIs occur frequently and rapidly after LT. Risk factors include female sex, pre-LT diabetes, increased post-LT ALT levels, and urethral catheter duration. CRKP infections, and not KPIs, affect mortality.

Key Words: Liver transplantation; *Klebsiella pneumoniae* infections; Carbapenem-resistant *Klebsiella pneumoniae*; Risk factors; Outcomes

Core Tip: Despite advances in liver transplantation (LT) technology, *Klebsiella pneumoniae* infections (KPIs) remain challenging to treat. Timely prevention of KPIs is therefore critical. Many risk factors play crucial roles in the occurrence of KPIs after LT and in determining recipient prognosis. We examined the role of KPIs in the prognosis of LT recipients and the risk factors for KPIs after LT. By analyzing the distribution of KPIs and drug resistance, we demonstrated that risk factors are associated with surgical operative variables. Identifying these risk factors provides a basis for preventing KPIs, which, in turn, may improve the prognosis of LT recipients.

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INTRODUCTION

Liver transplantation (LT) is the only curative treatment for end-stage liver disease[1]. However, the lifelong use of immunosuppressant drugs makes LT recipients susceptible to infection, which is the most common cause of early mortality after LT[2]. In recent years, studies have demonstrated that infections in LT recipients are more likely to be caused by gram-negative than gram-positive pathogens[3]. The gram-negative bacterium *Klebsiella pneumoniae* (*K. pneumoniae*) is a common cause of infection, with reports indicating that 6.9%-14.2% of LT recipients experienced bloodstream infections caused by this pathogen[4,5].

The major concern regarding *K. pneumoniae* infections (KPIs) is the incidence of carbapenem-resistant *K. pneumoniae* (CRKP), which ranges from 2.5% to 35%; CRKP-associated mortality is as high as 35%-83% among LT recipients[5-12]. Therapeutic options for these infections are limited.

Although some studies have demonstrated the effects of CRKP infection on the prognosis of solid organ transplant (SOT) recipients, the impact of KPIs or CRKP infections in LT recipients remains unclear[5,13,14]. The present study examined the drug resistance and distribution of *K. pneumoniae* isolates and the effect of KPIs, particularly CRKP infections, on outcomes after LT. The findings of this study should provide clues for preventing KPIs and improving the outcomes of LT recipients with KPIs.

MATERIALS AND METHODS

Study design and patient samples

We conducted a single-center retrospective study including all adult patients who underwent LT at The Third Xiangya Hospital of Central South University from January 1, 2015, to January 31, 2023. Four patients with donor-derived KPIs and two patients aged under 18 years were excluded from the analysis, along with two patients who died within 48 h of transplantation due to massive intraoperative blood loss or primary graft nonfunction. Finally, 405 patients who received donations after brain death and 1 patient who received a donation after circulatory death were included in the analysis. All LT recipients underwent modified piggyback LT. Induction immunosuppression consisted of corticosteroids with or without basiliximab, and maintenance immunosuppression involved a corticosteroid taper and tacrolimus/cyclosporin A with or without mycophenolate mofetil or enteric-coated mycophenolate sodium. Standard perioperative antibacterial prophylaxis consisted of third-generation cephalosporins or carbapenems administered for 3-5 d. Teicoplanin, caspofungin, and other antibiotics were prescribed according to the infection status and identified pathogens. Antithymocyte globulin was prescribed when acute rejection episodes were not resolved by glucocorticoid therapy or when glucocorticoids were unsuitable for preventing acute rejection. This study was approved by the Ethics Committee of The Third Xiangya Hospital (approval number: 24029) and conducted in accordance with the principles outlined in the Declaration of Helsinki.

Clinical data collection

All patients were routinely followed-up in the outpatient department post-LT. The clinical data of LT recipients aged ≥ 18 years were extracted from inpatient and outpatient electronic medical records, including demographic information and infection characteristics. The follow-up periods were 3 months for microbiological data and 6 months for mortality. We also analyzed the prevalence of KPIs and CRKP infections and lengths of intensive care unit (ICU) and hospital stays after LT. Analysis was performed to identify risk factors for KPIs, 6-month all-cause mortality, and ICU stays of at least 7 d after LT.

Definitions

Infections were defined using the standards of the Centers for Disease Control and Prevention/National Healthcare Safety Network[13]. Infection was confirmed based on a positive culture together with clinical signs of an active infection, including chills, fever, hypotension, or imaging findings from computed tomography or chest radiography. The source of infection was confirmed by a positive culture accompanied by clinical manifestations[13]. CRKP was defined as an insusceptibility to at least one carbapenem, with a minimum inhibitory concentration of ≥ 4 μg/mL for imipenem or meropenem (Clinical and Laboratory Standards Institute, 2017). Reoperations included both retransplantation and post-LT laparotomy. Acute rejection was determined by biopsy.

Microbiological studies

Patient samples, including blood, sputum, bronchoalveolar lavage fluid, urine, ascites, bile, organ preservation solution, and catheter drainage fluid, were collected for clinical bacterial culture. Sputum samples were obtained from the trachea or were induced. Blood, urine, sputum, and abdominal drainage fluid were subject to routine bacterial culture once a day for 5-7 d after LT. Samples were collected for culture when an infection was suspected within the 3 months following LT. Blood samples were cultured and analyzed using a BD9240 automatic blood culture instrument (BD, Franklin Lakes, NJ, United States).The identification and susceptibility tests for culture-positive cases were conducted according to standard bacteriological procedures using a Bruker mass spectrometer and VITEK® 2 system (bioMérieux, Marcyl'Étoile, France). The minimum inhibitory concentration as measured by agar dilution was used to assess the antimicrobial susceptibility of the bacteria. When analyzing drug resistance, all intermediates were classified as resistant.

Statistical analysis

Statistical analysis was performed using SPSS software version 26.0 (IBM Corporation, Armonk, NY, United States). Categorical variables are expressed as frequencies and percentages. Continuous variables with and without normal distributions are expressed as means ± SD and medians and interquartile ranges, respectively. Chi-squared tests or Fisher's exact tests were used to compare categorical variables. Binary logistic regression based on forward stepwise regression was used to identify risk factors using odds ratios (OR) and 95% confidence intervals (CI). Risk factors with P-values < 0.01 after univariate analysis were included in the multivariate analysis. Two-tailed P-values < 0.05 were considered statistically significant.

RESULTS

General patient characteristics and prognosis

The 406 LT recipients included in the analysis had a mean age of 47.3 ± 10.6 years with a median Model for End-Stage Liver Disease (MELD) score of 23.0; 17.7% of patients were female. Liver failure occurred as a result of hepatitis virus-related cirrhosis/necrosis/tumor (n = 304), alcoholic liver disease (n = 31), mixed cirrhosis (n = 19), autoimmune hepatitis (n = 15), primary biliary cirrhosis (n = 11), cryptogenic cirrhosis (n = 9), Budd-Chiari syndrome (n = 5), hepatolenticular degeneration (n = 3), failure of previous LT (n = 3), drug-induced liver injury (n = 2), polycystic liver (n = 2), and familial

hereditary amyloidosis (n = 2). Prior to LT, patients had a median creatinine level of 0.8 mg/dL, albumin level of 34.5 g/L, white blood cell count of 5.2 × 10^9/L, lymphocyte count of 0.8 × 10^9/L, and platelet count of 72.0 × 10^9/L. Two months before LT, 160 (39.4%) patients experienced infections, with 140 (34.5%) experiencing pulmonary infections and 13 (3.2%) experiencing multiple-site infections, all of which involved the lungs. The median surgical time, blood loss, and number of red blood cell (RBC) transfusions were 378.5 min, 3000.0 mL, and 12.0 units, respectively. In the 3 months following LT, 32 (7.9%) patients were infected with 44 strains of *K. pneumoniae*; 21 (65.6%) patients were infected with CRKP. The median time from transplantation to KPI onset was 7.5 d. After LT, 18 (4.4%) and 395 (97.3%) patients were treated with anti-thymocyte immunoglobulin and tacrolimus, respectively. The median alanine aminotransferase (ALT) and albumin levels on day 1 and the median creatinine level on day 3 after LT were 694.5 U/L, 37.2 g/L, and 0.9 mg/dL, respectively. Overall, 94 patients required mechanical ventilation, 19 required renal replacement therapy, and 67 experienced acute rejection after LT. Moreover, 17 (4.2%) patients underwent reoperation. The median postoperative ICU and hospital stays were 6.0 and 26.0 d, respectively. The 6-month mortality rate was 7.9% (n = 32). Rates of KPI and CRKP infection were significantly higher in patients who died (both 18.8%; n = 6/32) than in those who survived (7.0%; n = 26/374 and 4.0%; n = 15/374, respectively). The baseline demographic, clinical, and laboratory characteristics are summarized in Table 1.

Distribution and drug resistance of K. pneumoniae

The most common site of KPI was the lung/thoracic cavity (n = 15), followed by the bloodstream (n = 12) and abdominal/ biliary tract (n = 12) (Table 2).

The KPIs were resistant to the following antibiotics, from the highest to lowest rate: Piperacillin/tazobactam, levofloxacin, aztreonam, meropenem, cefepime, ceftazidime, cefoperazone/sulbactam, amikacin, trimethoprim/sulfamethoxazole, tigecycline, ceftazidime/avibactam, and polymixin B. Among the 44 *K. pneumoniae* isolates, 1 (2.3%) was resistant to ceftazidime/avibactam, 1 (2.3%) was resistant to polymixin B, and 10 (22.7%) were resistant to tigecycline (Table 3).

Analysis of the risk factors for KPIs after LT

Univariate logistic regression analysis of patients with and without KPIs identified female sex (P = 0.002), duration of surgery ≥ 450 min (P = 0.033), ALT level ≥ 1500 U/L 1 d after LT (P < 0.001), duration of post-LT urethral catheterization over 4 d (P = 0.009), and post-LT mechanical ventilation (P = 0.015) as risk factors for post-LT KPIs. A MELD score ≥ 22 at LT (P = 0.066), pre-LT diabetes (P = 0.067), infection in the 2 months prior to LT (P = 0.098), and anti-thymocyte globulin use (P = 0.063) showed a trend toward a higher incidence of KPIs but did not reach significance.

Multivariate analysis identified female sex (OR = 2.827, 95%CI: 1.256-6.364; P = 0.012), pre-LT diabetes (OR = 2.794, 95%CI: 1.070-7.294; P = 0.036), ALT level ≥ 1500 U/L 1 d after LT (OR = 3.645, 95%CI: 1.671-7.950; P = 0.001), and post-LT urethral catheter duration over 4 d (OR = 2.266, 95%CI: 1.016-5.054; P = 0.046) as independent risk factors for the development of post-LT KPIs. All data from the univariate and multivariate analyses are presented in Table 4.

Prognosis of patients with KPI or CRKP infection after LT

Pearson's chi-squared test was used to assess the effects of KPIs on the prognosis of LT recipients. Notably, patients with KPIs were more likely to have ICU stays of at least 7 d after LT than those without (56.3% *vs* 35.3%; P = 0.018). Patients with KPIs also had higher 6-month all-cause mortality than those without KPIs (17.6% *vs* 5.0%; P = 0.017). In contrast, patients with KPIs were not more likely to have post-LT hospitalization stays ≥ 21 d (P = 0.592) than those without (Table 5).

Univariate and multivariate analyses were performed to determine whether KPIs were independent risk factors for 6-month all-cause mortality. The multivariate analysis showed that KPIs were not a risk factor for 6-month all-cause mortality after LT. However, CRKP infections (OR = 5.330, 95%CI: 1.534-18.524; P = 0.008), female sex (OR = 2.829, 95%CI: 1.098-7.288; P = 0.031), intraoperative RBC transfusions ≥ 12 units (OR = 3.466, 95%CI: 1.259-9.543; P = 0.016), day 3 post-LT creatinine levels ≥ 2 mg/dL (OR = 9.724, 95%CI: 4.077-23.194; P < 0.001), and post-LT mechanical ventilation (OR = 4.118, 95%CI: 1.790-9.476; P = 0.001) were identified as risk factors for 6-month all-cause mortality after LT (Table 6).

Multivariate logistic regression analysis of factors related to prolonged ICU stays identified MELD scores ≥ 22 at LT (OR = 1.695, 95%CI: 1.086-2.645; P = 0.020), intraoperative blood loss ≥ 3000 mL (OR = 1.790, 95%CI: 1.139-2.813; P = 0.012), ALT levels ≥ 1500 U/L 1 d after LT (OR = 1.915, 95%CI: 1.123-3.265; P = 0.017), post-LT renal replacement therapy (OR = 4.058, 95%CI: 1.327-12.409; P = 0.014) and post-LT mechanical ventilation (OR = 3.402, 95%CI: 2.052-5.639; P < 0.001), but not KPIs or CRKP infections, as independent risk factors for post-LT ICU stays of at least 7 d (Table 7).

DISCUSSION

LT recipients are susceptible to opportunistic infections and antibiotic-resistant bacterial transmission due to malnutrition, complex surgical procedures, and immunosuppressive drugs[1]. *K. pneumoniae* is the most common gram-negative pathogen isolated from patients with LT[1]. In our study, the rates of KPI and CRKP infection were 7.9% and 5.2%, respectively, which were lower than the rates of 18.4% and 8.0%, respectively, reported by Liu *et al*[1] and Kalpoe *et al*[6].

K. pneumoniae most commonly infects the bloodstream and urinary tract post-LT[6,15]. Pneumonia, tertiary peritonitis, and surgical site infections have been reported as complications of KPIs in LT recipients[8,15]. The present study found that the lung/thoracic cavity was the most frequent site of infection, followed by the bloodstream, abdominal/biliary tract, urinary tract, perianal region, and liver.

Table 1 Demographic, laboratory, and clinical variables of 406 liver transplantation recipients

Characteristics	Value
Recipient age (yr), mean ± SD	47.3 ± 10.6
Recipient gender, no. of female (%)	72 (17.7)
Recipient BMI, median (IQR), kg/m^2	22.8 (20.8-25.1)
Hospital stay prior to LT, median (IQR), days	10.0 (1.0-22.3)
MELD score at LT, median (IQR)	23.0 (15.0-30.0)
Infection within 2 months prior to LT, *n* (%)	160 (39.4)
Pulmonary infection	140 (34.5)
Abdominal/biliary infection	6 (1.5)
Urinary tract infection	1 (0.2)
Multiple site infection[1]	13 (3.2)
Pre-LT use of broad-spectrum antibiotics	166 (40.9)
Underlying liver diseases, *n* (%)	406 (100)
Viral cirrhosis/necrosis/tumor	304 (74.9)
Alcoholic cirrhosis	31 (7.6)
Autoimmune hepatitis	15 (3.7)
Primary biliary cirrhosis	11 (2.7)
Mixed cirrhosis	19 (4.7)
Others[2]	26 (6.4)
Pre-LT type 2 diabetes, *n* (%)	48 (11.8)
Pre-LT creatinine, median (IQR), mg/dL	0.8 (0.7-1.0)
Pre-LT WBC count, median (IQR), × 10^9/L	5.2 (3.4-8.1)
Pre-LT lymphocyte count, median (IQR), × 10^9/L	0.8 (0.5-1.2)
Pre-LT platelet count, median (IQR), × 10^9/L	72 (43.8-106.5)
Pre-LT albumin level, median (IQR), g/L	34.5 (30.9-38.1)
Donor age (yr), mean ± SD	42.1 ± 13.0
Steatosis ≥ 30%, *n* (%)	42 (10.3)
Cold ischemia time, mean ± SD	6.2 ± 1.5
Duration of surgery, median (IQR), min	378.5 (333.0-425.0)
Intraoperative bleeding, median (IQR), mL	3000.0 (2000.0-5000.0)
Intraoperative RBC transfusion, median (IQR), units	12.0 (8.0-18.0)
Post-LT infections due to *Klebsiella pneumoniae*, *n* (%)	32 (7.9)
Post-LT infections due to CRKP, *n* (%)	21 (5.2)
Median interval between the onset of infections due to *Klebsiella pneumoniae* and LT, median (IQR), days	7.5 (2.0-17.8)
Post-LT immunosuppressant treatment, *n* (%)	406 (100)
Tacrolimus	395 (97.3)
Ciclosporin A	5 (1.2)
Mycophenolate mofetil/enteric-coated mycophenolate sodium	277 (68.2)
Sirolimus	5 (1.2)
Glucocorticoid	406 (100)
Basiliximab	214 (52.7)

Anti-thymocyte globulin	18 (4.4)
ALT on day 1 after LT, median (IQR), U/L	694.5 (383.0-1242.0)
Creatinine on day 3 after LT, median (IQR), mg/dL	0.9 (0.7-1.4)
Albumin level on day 1 after LT, median (IQR), g/L	37.2 (33.9-40.7)
Post-LT duration of urethral catheter, median (IQR), days	3.0 (2.0-5.0)
Post-LT mechanical ventilation, *n* (%)	94 (23.2)
Reoperation, *n* (%)	17 (4.2)
Acute rejection, *n* (%)	67 (16.5)
Post-LT renal replacement therapy, *n* (%)	19 (4.7)
ICU stay after LT, median (IQR), days	6.0 (5.0-7.0)
Hospitalization stay after LT, median (IQR), days	26.0 (21.0-30.0)
All-cause mortality within 6 months after LT, *n* (%)	32 (7.9)

[1]There were 9 cases of pulmonary and abdominal/bile duct infections, 1 case of pulmonary and urinary tract infections, 1 case of pulmonary and bloodstream infections, 1 case of pulmonary and intracranial infections, and 1 case each of pulmonary, abdominal and bloodstream infections.
[2]There were 9 cases of cryptogenic cirrhosis, 5 cases of Budd-Chiari syndrome, 3 cases each of hepatolenticular degeneration and transplant liver failure, 2 cases each of drug-induced liver injury, polycystic liver, and familial hereditary amyloidosis.
ALT: Alanine aminotransferase; BMI: Body mass index; ICU: Intensive care unit; Fis: Fungal infections; IQR: Interquartile range; LT: Liver transplantation; MELD: Model for End-Stage Liver Disease; RBC: Red blood cell.

Table 2 Infection sites of 44 episodes of infections caused by *Klebsiella pneumoniae*

Infection sites	Lung/thoracic cavity	Blood stream	Abdominal/biliary tract	Urinary tract	Perianal abscess	Liver abscess
Klebsiella pneumoniae (44)	15	12	12	3	1	1

Table 3 Rate of drug-resistance of 44 isolates of *Klebsiella pneumoniae* to 12 commonly used antibiotics, *n* (%)

Antimicrobial	n	Percentage
TZP	34	77.3
CAZ	31	70.5
CFS	30	68.2
FEP	31	70.5
ATM	31	70.5
MEM	31	70.5
AN	21	47.7
LVF	33	75.0
SXT	20	45.5
TIC	10	22.7
POL	1	2.3
CAZ/AVI	1	2.3

ATM: Aztreonam; TZP: Piperacillin/tazobactam; CFS: Cefoperazone/sulbactam; CAZ: Ceftazidime; FEP: Cefepime; AN: Amikacin; LVF: Levofloxacin; MEM: Meropenem; TIC: Tigecycline; SXT: Trimethoprim/sulfamethoxazole; POL: Polymixin B; CAZ/AVI: Ceftazidime/avibactam.

K. pneumoniae is a particularly concerning pathogen because it has limited antibiotic sensitivity and often develops multidrug resistance during treatment[16,17]. In our study, > 70% of the *K. pneumoniae* isolates were resistant to piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, or levofloxacin. The prevalence of CRKP infections was 5.2% in LT recipients, which is slightly lower than the rate of 7.0% reported in a previous study on LT recipients in China[1]. The rate of *K. pneumoniae* resistance to carbapenems reached 70.5%, which is similar to the rate of 63.3% re-

Table 4 Univariate and multivariate logistic regression analysis of risk factors for infections due to *Klebsiella pneumoniae* within 3 months after liver transplantation, *n* (%)

Variables	With *K. pneumoniae* infections(32)	Without *K. pneumoniae* infections(374)	*P* value	OR (95%CI)
Total				
Univariate analysis				
Female sex	12 (37.5)	60 (16.0)	0.002	
Recipient age ≥ 55 yr	10 (31.3)	91 (24.3)	0.385	
Recipient BMI ≥ 25	9 (28.1)	97 (25.9)	0.787	
MELD score at LT ≥ 22	23 (71.9)	206 (55.1)	0.066	
Hospital stay prior to LT ≥ 7 d	23 (71.9)	216 (57.8)	0.119	
Viral cirrhosis/necrosis/tumor	21 (65.6)	283 (75.7)	0.209	
Alcoholic cirrhosis	3 (9.4)	28 (7.5)	0.969	
Pre-LT diabetes	7 (21.9)	41 (11.0)	0.067	
Pre-LT use of broad-spectrum antibiotics ≥ 3 d	16 (50.0)	150 (40.1)	0.275	
Pre-LT creatinine ≥ 2 mg/dL	1 (3.1)	28 (7.5)	0.574	
Infection within 2 months prior to LT	17 (53.7)	143 (38.2)	0.098	
Pre-LT WBC count ≥ 10 × 10^9/L	4 (12.5)	55 (14.7)	0.937	
Pre-LT lymphocyte count ≤ 0.5 × 10^9/L	6 (18.8)	92 (24.6)	0.458	
Pre-LT platelet count ≤ 50 × 10^9/L	12 (37.5)	123 (32.9)	0.595	
Pre-LT albumin level < 30 g/L	9 (28.1)	71 (19.0)	0.212	
Donor age ≥ 50 yr	13 (40.6)	121 (32.4)	0.340	
Steatosis ≥ 30%	2 (6.3)	40 (10.7)	0.624	
Cold ischemia time ≥ 360 min	15 (46.9)	189 (50.5)	0.691	
Duration of surgery ≥ 450 min	10 (31.3)	61 (16.3)	0.033	
Intraoperative bleeding ≥ 3000 mL	23 (71.9)	214 (57.2)	0.101	
Intraoperative RBC transfusion ≥ 12 U	20 (62.5)	201 (53.7)	0.340	
ALT on day 1 after LT ≥ 1500U/L	14 (43.8)	66 (17.6)	<0.001	
Creatinine on day 3 after LT ≥ 2 mg/dL	4 (12.5)	57 (15.2)	0.874	
Albumin level on day 1 after LT < 30 g/L	4 (12.5)	24 (6.4)	0.347	
Post-LT duration of urethral catheter ≥ 4 d	22 (68.8)	167 (44.7)	0.009	
Post-LT mechanical ventilation	13 (40.6)	81 (21.7)	0.015	
Reoperation	3 (9.4)	14 (3.7)	0.286	
Acute rejection	6 (18.8)	61 (16.3)	0.721	
Post-LT renal replacement therapy	3 (9.4)	16 (4.3)	0.382	
Glucocorticoidse ≥ 1500 mg	21 (65.6)	235 (62.8)	0.754	
Basiliximab use ≥ 40 mg	14 (43.8)	145 (38.8)	0.580	
Anti-thymocyte globulin use	4 (12.5)	14 (3.7)	0.063	
Multivariate analysis				
Female sex			0.012	2.827 (1.256-6.364)
Pre-LT diabetes			0.036	2.794 (1.070-7.294)

ALT on day 1 after LT ≥ 1500U/L	0.001	3.645 (1.671-7.950)
Post-LT duration of urethral catheter ≥ 4 d	0.046	2.266 (1.016-5.054)

ALT: Alanine aminotransferase; BSIs: Bloodstream infections; CI: Confidence intervals; LT: Liver transplantation; MELD: Model for End-Stage Liver Disease; OR: Odds ratios; RBC: Red blood cell; BMI: Body mass index; *K. pneumoniae*: *Klebsiella pneumoniae*.

Table 5 The postoperative outcome for patients with/without infections caused by *Klebsiella pneumoniae* following liver transplantation, *n* (%)

Variables	With infections caused by *K. pneumoniae*(32)	Without infections caused by *K. pneumoniae* (374)	X^2	*P* value
ICU stay after LT ≥ 7 d	18 (56.3)	132 (35.3)	5.557	0.018
Hospitalization stay after LT ≥ 21 d	26 (81.3)	302 (80.7)	0.288	0.592
All-cause mortality within 6 months after LT	6 (18.8)	32 (8.6)	5.651	0.017

ICU: Intensive care unit; LT: Liver transplantation; *K. pneumoniae*: *Klebsiella pneumoniae*

ported by Liu *et al*[1]. Previous retrospective studies recommend polymyxin E, amikacin, and tigecycline for SOT recipients with CRKP infections[18,19]. However, the existing options (polymyxins, aminoglycosides, tigecycline, and carbapenems) for carbapenem-resistant Enterobacteriaceae are limited by their low efficacy, resistance, suboptimal pharmacokinetics, and high toxicity rates[20,21]. Our results identified ceftazidime/avibactam and polymyxin B as the first choice for KPI treatment, with tigecycline the second choice. The CRKP infection rate in patients who died was significantly higher than that in patients who survived in our study, which is consistent with previous studies that identified CRKP infections as the most lethal among all gram-negative infections in SOT recipients[22,23].

Previous studies have demonstrated the following risk factors for CRKP infections in LT recipients: Colonization with CRKP, hepatocellular carcinoma, chronic kidney disease, preoperative infection, MELD score > 20, mechanical ventilation, exposure to cephalosporine-carbapenem/piperacillin-tazobactam, renal replacement therapy, hepatitis C virus recurrence, length of ICU stay, and Roux-en-Y biliary choledochojejunostomy[1,8,11,15].

Our analysis demonstrated that pre-LT diabetes is independently associated with the development of post-LT KPIs. The underlying mechanism may involve diabetes-induced immunosuppression. A previous study established a relationship between the risk factors of necrotizing soft tissue *Klebsiella* infections and diabetes mellitus[24]. Singh *et al*[25] revealed that diabetes mellitus is an independent and significant predictor of bacteremia in LT recipients.

We also revealed a post-LT urethral catheter duration of > 4 d to be an independent risk factor for post-LT KPIs. A univariate analysis performed by Zhang *et al*[26] suggested an association between urinary catheterization and bacterial and fungal infections after LT; however, this association was lost following multivariate analysis.

We identified female sex as a risk factor for KPIs, consistent with the findings of a study by Abbott *et al*[27], which claimed that females are more likely to be hospitalized for septicemia following kidney transplantation. In contrast, Bert *et al*[28] found male sex to be significantly associated with bloodstream infections post-LT. The most likely cause of the increased risk of KPIs in female LT recipients is their greater vulnerability to urinary tract infections. However, only 3 of the 44 *K. pneumoniae* strains in our study involved urinary tract infections. The reason for this is unclear, and therefore confirmation that the prolonged use of urethral catheters and female sex are independent risk factors for post-LT KPIs is required in further larger-sample studies.

Elevated post-LT ALT levels were also found to be an independent risk factor for post-LT KPIs. To the best of our knowledge, this is the first study to identify this risk factor, which resulted in a 3.6-fold increased risk of post-LT KPIs [28]. Higher ALT levels early after LT indicate severe intraoperative blood loss or hypotension or poor graft quality, all of which render LT recipients more susceptible to infection.

The present study revealed that KPIs have no impact on ICU or hospital stays or 6-month all-cause mortality rates. However, 6-month all-cause mortality is impacted by CRKP infections, in addition to female sex, intraoperative RBC transfusion, day 3 post-LT creatinine level, and post-LT mechanical ventilation. These results are consistent with those of a previous study that identified mechanical ventilation and CRKP infections as risk factors for three-month mortality after LT[1]. Previous studies have also shown that CRKP infections are independently associated with mortality rates in SOT recipients, which range from 40% to 75%[1,23,29,30].

Limitations of the study

This study has several limitations. First, the retrospective single-center design implies an inherent selection bias and represents only the regional prevalence of KPIs and CRKP infections in LT recipients. Second, many studies have stated that colonization with *K. pneumoniae*, particularly CRKP, prior to LT may be important for the risk of post-LT KPIs and CRKP infections. Unfortunately, surveillance for *K. pneumoniae* is not routinely performed at our center.

Table 6 Univariate and multivariate Logistic regression analysis of risk factors for 6-month all-cause mortality after liver transplantation, *n* (%)

Variables	Death(32)	Survival(374)	*P* value	OR (95%CI)
Total				
Univariate analysis				
Female sex	10 (31.3)	62 (16.6)	0.037	
Recipient age ≥ 55 yr	14 (43.8)	87 (23.3)	0.010	
Recipient BMI ≥ 25	4 (12.5)	102 (27.3)	0.068	
MELD score at LT ≥ 22	24 (75.0)	205 (54.8)	0.027	
Hospital stay prior to LT ≥ 7 d	24 (75.0)	215 (57.5)	0.053	
Viral cirrhosis/necrosis/tumor	25 (78.1)	279 (74.6)	0.659	
Alcoholic cirrhosis	1 (3.1)	30 (8.0)	0.513	
Pre-LT diabetes	4 (12.5)	44 (11.8)	1.000	
Pre-LT creatinine ≥ 2 mg/dL	6 (18.8)	23 (6.1)	0.008	
Infection within 2 months prior to LT	19 (59.4)	141 (37.7)	0.016	
Pre-LT WBC count ≥ 10×10^9/L	7 (21.9)	52 (13.9)	0.219	
Pre-LT lymphocyte count ≤ 0.5×10^9/L	12 (37.5)	86 (23.0)	0.066	
Pre-LT platelet count ≤ 50×10^9/L	8 (25.0)	127 (34.0)	0.302	
Pre-LT albumin level < 30g/L	6 (18.8)	74 (19.8)	0.888	
Donor age ≥ 50 yr	7 (21.9)	127 (34.0)	0.163	
Steatosis ≥ 30%	3 (9.4)	39 (10.4)	1.000	
Cold ischemia time ≥ 360 min	20 (62.5)	199 (53.2)	0.248	
Duration of surgery ≥ 450 min	8 (25.0)	63 (16.8)	0.244	
Intraoperative bleeding ≥ 3000 mL	26 (81.3)	211 (56.4)	0.006	
Intraoperative RBC transfusion ≥ 12 U	25 (78.1)	196 (52.4)	0.005	
ALT on day 1 after LT ≥ 1500 U/L	8 (25.0)	72 (19.3)	0.433	
Creatinine on day 3 after LT ≥ 2 mg/dL	18 (56.3)	43 (11.5)	< 0.001	
Albumin level on day 1 after LT < 30 g/L	6 (18.8)	25 (6.7)	0.564	
Post-LT infections due to *Klebsiella pneumoniae*	6 (18.8)	26 (7.0)	0.017	
Post-LT infections due to CRKP	6 (18.8)	15 (4.0)	< 0.001	
Post-LT mechanical ventilation	19 (59.4)	75 (20.1)	< 0.001	
Reoperation	3 (9.4)	14 (3.7)	0.286	
Acute rejection	4 (12.5)	63 (16.8)	0.525	
Post-LT renal replacement therapy	8 (25.0)	11 (2.9)	< 0.001	
Glucocorticoidse ≥ 1500 mg	19 (59.4)	237 (63.4)	0.653	
Basiliximab use ≥ 40 mg	10 (31.3)	149 (39.8)	0.339	
Anti-thymocyte globulin use	1 (3.1)	17 (4.5)	1.000	
Multivariate analysis				
Female sex			0.031	2.829 (1.098-7.288)
Intraoperative RBC transfusion ≥ 12 U			0.016	3.466 (1.259-9.543)
Creatinine on day 3 after LT ≥ 2 mg/dL			< 0.001	9.724 (4.077-23.194)
Post-LT infections due to CRKP			0.008	5.330 (1.534-18.524)
Post-LT mechanical ventilation			0.001	4.118 (1.790-9.476)

ALT: Alanine aminotransferase; CI: Confidence intervals; LT: Liver transplantation; RBC: Red blood cell; MELD: Model for End-Stage Liver Disease; OR: Odds ratios; BMI: Body mass index.

Table 7 Univariate and multivariate Logistic regression analysis of risk factors for intensive care unit stay after liver transplantation ≥ 7, *n* (%)

Variables	ICU stay after LT ≥ 7 d (150)	ICU stay after LT < 7 d (256)	*P* value	OR (95%CI)
Total				
Univariate analysis				
Female sex	34 (22.7)	38 (14.8)	0.046	
Recipient age ≥ 55 yr	45 (30.0)	56 (21.9)	0.068	
Recipient BMI ≥ 25	38 (25.3)	68 (26.6)	0.785	
MELD score at LT ≥ 22	98 (65.3)	131 (51.2)	0.005	
Hospital stay prior to LT ≥ 7 d	98 (65.3)	141 (55.1)	0.043	
Viral cirrhosis/necrosis/tumor	112 (74.7)	192 (75.0)	0.940	
Alcoholic cirrhosis	11 (7.3)	20 (7.8)	0.861	
Pre-LT diabetes	17 (11.3)	31 (12.1)	0.815	
Pre-LT creatinine ≥ 2 mg/dL	18 (12.0)	11 (4.3)	0.004	
Infection within 2 months prior to LT	57 (38.0)	103 (40.2)	0.657	
Pre-LT WBC count ≥ 10×10^9/L	27 (18.0)	123 (48.0)	0.129	
Pre-LT lymphocyte count ≤ 0.5×10^9/L	34 (22.7)	64 (25.0)	0.596	
Pre-LT platelet count ≤ 50×10^9/L	46 (30.7)	89 (34.8)	0.397	
Pre-LT albumin level < 30 g/L	28 (18.7)	123 (48.0)	0.687	
Donor age ≥ 50 yr	46 (30.7)	88 (34.4)	0.443	
Steatosis ≥ 30%	16 (10.7)	26 (10.2)	0.871	
Cold ischemia time ≥ 360 min	78 (52.0)	136 (53.1)	0.827	
Duration of surgery ≥ 450 min	31 (20.7)	40 (15.6)	0.197	
Intraoperative bleeding ≥ 3000 ml	102 (68.0)	135 (52.7)	0.003	
Intraoperative RBC transfusion ≥ 12 U	92 (61.3)	129 (50.4)	0.033	
ALT on day 1 after LT ≥ 1500 U/L	41 (27.3)	39 (15.2)	0.003	
Creatinine on day 3 after LT ≥ 2 mg/dL	30 (20.0)	31 (12.1)	0.032	
Albumin level on day 1 after LT < 30 g/L	12 (8.0)	16 (6.3)	0.502	
Post-LT infections due to *Klebsiella pneumoniae*	18 (12.0)	14 (5.5)	0.018	
Post-LT infections due to CRKP	15 (10.0)	6 (2.3)	0.001	
Post-LT mechanical ventilation	59 (39.3)	35 (13.7)	< 0.001	
Reoperation	11 (7.3)	6 (2.3)	0.015	
Acute rejection	28 (18.7)	39 (15.2)	0.369	
Post-LT renal replacement therapy	14 (9.3)	5 (2.0)	0.001	
Glucocorticoidse ≥ 1500 mg	102 (68.0)	154 (60.2)	0.114	
Basiliximab use ≥ 40 mg	55 (36.7)	104 (40.6)	0.430	
Anti-thymocyte globulin use	7 (4.7)	11 (4.3)	0.861	
Multivariate analysis				
MELD score at LT ≥ 22			0.020	1.695 (1.086-2.645)

Intraoperative bleeding ≥ 3000 ml	0.012	1.790 (1.139-2.813)
ALT on day 1 after LT ≥ 1500 U/L	0.017	1.915 (1.123-3.265)
Post-LT renal replacement therapy	0.014	4.058 (1.327-12.409)
Post-LT mechanical ventilation	< 0.001	3.402 (2.052-5.639)

ICU: Intensive care unit; ALT: Alanine aminotransferase; CI: Confidence intervals; LT: Liver transplantation; RBC: Red blood cell; MELD: Model for End-Stage Liver Disease; OR: Odds ratios; CRKP: Carbapenem-resistant *Klebsiella pneumoniae*; BMI: Body mass index.

CONCLUSION

The homogeneity of infections caused by *K. pneumoniae* may lead to an accurate analysis of the risk factors for KPIs and mortality. Although our study included a relatively large cohort of LT recipients, the effect of KPIs, particularly CRKP infections, on patient outcomes emphasizes the need for further prospective studies. Given that the antimicrobial treatment of KPIs, especially CRKP infections, remains an ongoing challenge, knowledge of the risk factors for these infections and implementation of enhanced infection control measures are essential for successful LT.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation (LT) is the only curative treatment available for end-stage liver disease. However, LT recipients are prone to many types of infections, which are the most common cause of early mortality after LT. Recent studies have demonstrated that LT recipients suffer from bloodstream infections caused by *K. pneumoniae*. In addition, there has been little discussion on the adverse impacts of *K. pneumoniae* infections (KPIs) or carbapenem-resistant *K. pneumoniae* (CRKP) infections among LT recipients.

Research motivation

The key to retrospective cohort studies is to explore the risk factors for the development of KPIs in patients after LT and analyze drug resistance. Careful follow-up is required to minimize the occurrence of KPIs in patients with LT, reduce the development of drug resistance, and improve patient survival and prognosis.

Research objectives

The primary objective of this study was to assess the incidence, timing, distribution, drug resistance, and risk factors of KPIs within 3 months of LT. The secondary objective was to evaluate the impact of KPIs, particularly CRKP, on outcomes.

Research methods

In total, 406 patients undergoing LT between January 2015 and January 2023 were included in the present retrospective study to investigate the risk factors for KPIs and assess the impact of KPIs and CRKP on the prognosis of LT recipients using logistic regression.

Research results

Of the 406 LT recipients recruited, 32 (7.9%) were infected with 44 strains of *K. pneumoniae* within 3 months post-LT. Of the 32 patients, 21 (65.6%) were infected with CRKP. The median time from LT to KPI onset was 7.5 d. KPIs (18.8%, 6/32) and CRKP infection (18.8%, 6/32) rates were significantly higher in patients who died than in those who survived (7.0%, 26/374 and 4.0%, 15/374, respectively). The multivariate analysis identified female sex [odds ratio (OR) = 2.827, 95% confidence interval (CI): 1.256-6.364, P = 0.012], pre-LT diabetes [OR = 2.794, 95%CI: 1.070-7.294, P = 0.036], day 1 post-LT alanine aminotransferase levels ≥ 1500 U/L (OR = 3.645, 95%CI: 1.671-7.950, P = 0.001), and post-LT urethral catheter durations > 4 d (OR = 2.266, 95%CI: 1.016-5.054, P = 0.046) were independently associated with the development of post-LT KPIs. On the prognosis of patients with LT, patients with KPIs were more likely to stay in the intensive care unit ≥ 7 d after LT than those without KPIs (56.3% *vs* 35.3%; P = 0.018). Patients with KPIs had a higher 6-month all-cause mortality rate than those without KPIs (17.6% *vs* 5.0%; P = 0.017). The multivariate analysis showed that KPIs were not risk factors for 6-month all-cause mortal-ity after LT. However, infections caused by CRKP (OR = 1.534-18.524, 95%CI: 5.330, P = 0.008), female sex (OR = 2.829, 95%CI: 1.098-7.288, P = 0.031), intraoperative red blood cell transfusion ≥ 12 U (OR = 3.466, 95%CI: 1.259-9.543, P = 0.016), day 3 post-LT creatinine levels ≥ 2 mg/dL (OR = 9.724, 95%CI: 4.077-23.194, P < 0.001) and post-LT mechanical ventilation (OR = 4.118, 95%CI: 1.790-9.476, P = 0.001) were risk factors for 6-month all-cause mortality after LT.

Research conclusions

This novel retrospective assessment explored key factors in the prevention of KPIs or CRKP. Many risk factors play crucial roles in the development of KPIs after LT and in recipient prognosis. This study explored the role of KPIs in the

prognosis of LT recipients and the risk factors for all KPIs after LT. By analyzing the distribution of KPIs and drug resistance, we demonstrated that risk factors are associated with surgical variables. Identifying these risk factors provides a basis for the prevention of KPIs, thereby improving the prognosis of LT recipients.

Research perspectives

In future studies, we should obtain more data to more accurately identify other potential correlates of KPIs in patients with LT to reduce the occurrence of KPIs. In addition, monitoring *K. pneumoniae*, especially CRKP, colonization before LT may provide new insights.

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