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Retrospective Cohort Study

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

Klebsiella pneumoniae infections after liver transplantation

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Abstract

BACKGROUND

Live transplantation (LT) is the only available curative treatment for end-stage liver disease. However, LT recipients are prone to 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 *Klebsiella pneumoniae* and the adverse effects of *K. pneumoniae* infections (KPIs) or carbapenem-resistant *K. pneumoniae* (CRKP) infections among LT recipients are unclear.

AIM

To assess KPI incidence, timing, distribution, drug resistance, and risk factors within 3-months post-LT and evaluate KPIs/CRKP impact on outcomes

METHODS

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

RESULTS

The KPI incidence was 7.9% (32/406); the median time from LT to KPI onset was 7.5 days. The lung/thoracic cavity was the most frequently KPI-infected site. Of 44 *K. pneumoniae* isolates, 43 (97.7%) were susceptible to polymyxin B or ceftazidime/avibactam; 34 (77.3%) were susceptible to tigecycline. However, >70% of isolates were resistant to piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, and levofloxacin. Multivariate analysis identified that 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], 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 associated with post-LT KPI. In univariate analysis, KPIs were related to intensive care unit stays ≥7 days and 6-month all-cause mortality post-LT. Multivariate analysis showed CRKP infections, not KPIs, adversely impacted 6-month all-cause mortality post-LT.

CONCLUSION

Post-LT KPIs occur frequently, with short onsets. Risk factors include female sex, pre-LT diabetes, and increased post-LT alanine aminotransferase levels and urethral catheter durations. CRKP infections, not KPIs, affect mortality.

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

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Core Tip: Despite advances in LT technology, KPIs remain challenging. Timely prevention of KPIs is critical. Many risk factors play crucial roles in the occurrence of

KPIs after LT and in determining recipient prognosis. This study examined the role of KPIs in the prognosis of liver transplant 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, improves the prognosis of LT recipients.

INTRODUCTION

Live transplantation (LT) is the only curative treatment for end-stage liver disease[1]. However, because of the lifelong use of immunosuppressants, LT recipients are prone to many types of infections, which are the most common causes of early mortality after LT[2]. In recent years, studies have demonstrated that gram-negative pathogens are more responsible for infections in LT recipients than gram-positive pathogens[3]. Previous studies reported that 6.9%–14.2% of LT recipients experienced bloodstream infections caused by *K. pneumonia*[4, 5].

The major concern regarding the outcomes associated with *Klebsiella pneumoniae* infections (KPIs) is that the incidence of carbapenem-resistant *K. pneumoniae* (CRKP) infection ranges from 2.5% to-35%, and the CRKP-associated mortality rate is as high as 35%-83% among LT recipients[5-12]. However, therapeutic options for infections caused by these bacteria are limited.

Although some studies have demonstrated the effects of CRKP on the prognosis of solid organ transplant (SOT) recipients, the adverse impact of KPIs or CRKP infections among LT recipients is unclear[5, 13, 14]. The present study examined the drug resistance and distribution of *K. pneumoniae* isolates and the timing, risk factors, and influence of KPIs, particularly CRKP, on outcomes after LT. We identified antibiotic resistance and risk factors for KPIs and the effects of KPIs to provide clues for preventing KPIs and improving the outcomes of LT with KPIs.

MATERIALS AND METHODS

Study design and patient sample

We conducted a single-center retrospective study including all adult patients with 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 younger than 18 years of age were excluded, along with two patients who died within 48 h due to massive blood loss during the operation or primary graft nonfunction. Finally, 405 patients undergoing LT from brain-dead donors and 1 patient from a heart-dead donor were recruited. All LT recipients underwent modified piggyback LT. Immunosuppression consisted of induction with corticosteroids with or without basiliximab, followed by maintenance with 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 for 3-5 days. Teicoplanin, caspofungin, and other antibiotics were prescribed according to the infection status and pathogens identified. Antithymocyte globulin was prescribed when acute rejection did not respond to glucocorticoid therapy or when glucocorticoids were unsuitable for preventing acute rejection. This study was approved by the Ethics Committee of the Third Xiangya Hospital and conducted in accordance with the principles of 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 >8 years were extracted from inpatient and outpatient electronic medical records, including demographics, infection characteristics, and other clinical variables. All LT recipients were followed up for 3 months for microbiological data and 6 months for mortality. We also investigated the prevalence of KPIs and CRKP infections and lengths of intensive care unit (ICU) and hospital stays after LT. The risk factors for KPIs, 6-month all-cause mortality, and length of ICU stay of ≥7 days after LT were analyzed.

Definitions

Infections were defined using the standards of the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN)[13]. Infection was confirmed based on a positive culture together with clinical signs of an active infection (e.g., chills, fever, hypotension, or imaging such as CT or chest X-ray). The source of infection was defined as a culture-positive site of infection accompanied by positive clinical manifestations[13]. CRKP was defined as an insusceptibility to at least one carbapenem, with a minimum inhibitory concentration ≥4 ug/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.

Microbiologic studies

Samples were collected for clinical bacterial culture, including blood, sputum, bronchoalveolar lavage fluid, urine, ascites, bile, organ preservation solution, and catheter drainage fluid. Sputum samples were from the trachea or induced sputum. Blood, urine, sputum, and abdominal drainage fluid were routinely cultured for bacteria once a day for 5–7 days after LT. Clinical samples were collected for culture when any infection was suspected within 3 months after LT. Blood samples were cultured and monitored using a BD9240 automatic blood culture instrument (Becton Dickinson, USA). According to standard bacteriological procedures, the identification and susceptibility tests for culture-positive cases were conducted using Bruker mass spectrometer and Vitek-2 system (bioMérieux, Marcyl'Etoile, France). The minimum inhibitory concentration measured by agar dilution was used to test the antimicrobial susceptibility of the bacteria. When analyzing drug resistance, all intermediates were classified as resistant.

Statistical analyses

Statistical analysis was performed using SPSS software (version 26.0; SPSS, Inc., Chicago, IL, USA). Categorical variables are expressed as frequencies and percentages. Continuous variables with or without normal distributions are described as the means±standard deviations or the medians and interquartile ranges (IQRs), respectively. We used the chi-squared test or Fisher's exact test for categorical variables. Risk factors with *P*-values <0.01 in univariate analysis were included in the multivariate analysis. Binary logistic regression based on forward stepwise regression was used to determine risk factors using odds ratios (ORs) and 95% confidence intervals (CIs). Two-tailed *P*-values <0.05 were considered statistically significant.

RESULTS

General characteristics and prognosis of LT recipients

Of the 406 LT recipients recruited, 17.7% were female. The mean age of all patients was 47.3 (±10.6) years, with a median MELD score of 23.0. Patients were diagnosed with 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), transplanted liver failure (n = 3), drug-induced liver injury (n = 2), polycystic liver (n = 2), and familial hereditary amyloidosis (n = 2), with a median creatinine level of 0.8 mg/dL, albumin level of 34.5 g/L, white blood cell (WBC) count of 5.2×10^9/L, lymphocyte count of 0.8×10^9/L, and platelet count of 72.0×10^9/L preceding LT. Two months before LT, 39.4% (160/406) of patients experienced infections, with 140 (34.5%) experiencing pulmonary infections and 13 (3.2%) experiencing multiple-sites infections, all of whom had pulmonary infections. 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. Within 3-months post-LT, 32 (7.9%) patients were infected with 44 strains of *K. pneumoniae*, of which 21 (65.6%) were infected with CRKP. The median time from transplantation to KPIs was 7.5 days. 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 had acute rejection after LT. Moreover, 4.2% (17/406) of patients underwent reoperation. The median postoperative ICU and hospital lengths of stay were 6.0 and 26.0 days, respectively. The 6-month mortality for LT was 7.9% (32/406). 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 baseline demographic, clinical, and laboratory characteristics are described in Table 1.

Distribution and drug resistance of pathogens

The most common infection site in the 44 KPIs was the lung/thoracic cavity (n = 15), followed by the bloodstream (n = 12) and abdominal/biliary tract (n = 12) (Table 2).

The KPI 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 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

Patients with and without KPIs were compared. By univariate logistic regression, female sex (P=0.002), duration of surgery ≥450 min (P=0.033), ALT level 1 day after LT ≥1500 U/L (P<0.001), post-LT urethral catheter duration ≥4 days (P=0.009), and the need for post-LT mechanical ventilation (P=0.015) were associated with an increased risk for post-LT KPIs. A MELD score at LT ≥22 (P=0.066), pre-LT diabetes (P=0.067), infection within 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.

Finally, the 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 1 day 1 LT ≥1500 U/L [OR=3.645, 95%CI:1.671-7.950, *P*=0.001], and post-LT urethral catheter duration >4 d [OR=2.266, 95%CI:1.016-5.054, *P*=0.046] were independently associated with the development of post-LT KPIs. All data from the univariate and multivariate analyses are shown in Table 4.

Prognosis of patients with KPIs or CRKP after LT

Pearson's chi-square 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 ≥7 days after LT than those without (56.3% *vs* 35.3%; *P*=0.018). Patients with KPIs had higher 6-month all-cause mortality rates than those without KPIs (17.6% *vs* 5.0%; *P*=0.017). In contrast, KPIs were not correlated with post-LT hospitalization stays ≥21 days (*P*=0.592), when compared to non-KPIs (Table 5).

Univariate and multivariate analyses of potential risk factors for mortality were performed to determine whether KPIs were independent risk factors for 6-month all-cause mortality. The multivariate analysis showed that KPIs were not risk factors for 6-month all-cause mortality after LT. However, CRKP infections [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 RBC transfusions ≥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 identified as risk factors for 6-month all-cause mortality after LT (Table 6).

Likewise, when factors related to prolonged ICU stays were analyzed, multivariate logistic regression analysis identified MELD scores at LT ≥22 [OR=1.695, 95%CI:1.086-2.645, *P*=0.020], intraoperative bleeding ≥3000 mL [OR=1.790, 95%CI:1.139-2.813, *P*=0.012], ALT levels 1 day after LT ≥1500 U/L [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 the need for post-LT mechanical ventilation [OR=3.402, 95%CI:2.052-5.639, *P*<0.001], not

KPIs or CRKP infections, as independent risk factors for post-LT ICU stays ≥7 days (Table 7).

DISCUSSION

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

Blood stream and urinary tract infections are the most common post-LT KPIs[6, 15]. Moreover, pneumonia, tertiary peritonitis, and surgical site infections have been reported as other KPI complications in LT recipients[8, 15]. The present study found that the lung/thoracic cavity was the most frequently infected site, followed by the bloodstream, abdominal/biliary tract, urinary tract, perianal region, and liver.

pneumoniae is particularly concerning 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 another study on LT recipients in China[1]. The rate of *K. pneumoniae* drug resistance to carbapenems reached 70.5%, which is similar to the 63.3% rate reported by Liu *et al.*[1] According to previous retrospective studies, polymyxin E, amikacin, and tigecycline are recommended as the optimal drugs 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 showed that ceftazidime/avibactam and polymyxin B is the best choices, while

tigecycline is the next-best choice for KPI treatment. The CRKP infection rate (18.8%, 6/32) in patients who died was significantly higher than that in patients who survived (4.0%, 15/374) in our study, which is consistent with studies demonstrating that CRKP infections are 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 cephalosporinecarbapenem/piperacillin-tazobactam, renal replacement therapy, HCV recurrence, length of ICU stay, and Roux-en-Y biliary choledochojejunostomy[1, 8, 11, 15].

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

We revealed that a post-LT urethral catheter duration >4 days is an independent risk factor for post-LT KPIs. Zhang *et al*. suggested an association between urinary catheterization and infections in the univariate analysis of bacterial and fungal infections after LT; however, this association was not confirmed by multivariate analysis[26].

We found that female sex is a risk factor for KPIs, in line with a study by Abbott *et al*., which claimed that female sex is associated with hospitalization for septicemia among kidney transplant recipients[27]. Our findings are in contrast with the findings of Bert *et al*., which suggested that male sex is 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 KPI strains involved urinary tract infections in our study. The reason for this is unclear, and prolonged use of urethral catheters and female sex as independent risk factors for post-LT KPIs require further larger-sample studies for confirmation.

We also found that elevated post-LT ALT levels are 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 for post-LT KPIs[28]. A higher ALT level in the early stage of liver transplantation indicates a severe attack caused by the operation due to massive bleeding or severe hypotension during the operation or poor donor quality. All these situations enable LT recipients to easily develop infections.

Our present revealed that KPIs have no impact on ICU and hospital lengths of stay and 6-month all-cause mortality rates. However, CRKP infections impact 6-month all-cause mortality, in addition to other risk factors such as female sex, intraoperative RBC transfusion, day 3 post-LT creatinine level, and post-LT mechanical ventilation, which agrees with a previous study claiming that mechanical ventilation and CRKP infection are risk factors closely related to 3-month mortality after LT[1]. Previous studies have also shown that CRKP infection is independently associated with SOT recipient mortality rates, which range from 40% to 75%[1, 23, 29, 30].

Limits of the study

This study had 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.

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 comparably large cohort of LT recipients, the effect of KPIs, particularly CRKP infections, on the outcomes of LT recipients 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

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 KPIs or 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 was 7.5 days. 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 [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], day 1 post-LT ALT 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 ICU ≥7 days 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 mortality 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 RBC 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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