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ORIGINAL RESEARCH

Risk Factors and Outcomes of Carbapenem-Resistant Enterobacteriaceae Infection After Liver Transplantation: A Retrospective Study in a Chinese Population

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Background: There is an increasing prevalence of carbapenem-resistant Enterobacteriaceae (CRE) infection after liver transplantation (LT). Improved understanding of the risk factors and outcomes of CRE infections can help us to develop effective preventive strategies and even guide early treatment of high-risk LT patients.

Methods: This was a retrospective study involving all Chinese adult patients who underwent LT between December 2017 and September 2019 in our center. We analyzed the possible risk factors and outcomes associated with CRE infections in the first 30 days post-LT.

Results: A total of 387 patients underwent LT. Among them, 26 patients (6.7%) developed CRE infections within 30 days after transplantation. Patients with CRE infections had significantly lower 30-day and 180-day survival rates (80.8% vs 96.4%, $p<0.001$; 51.5% vs 92.4%, $p<0.001$). Multivariate analysis identified that intraoperative blood loss equal to or more than 1500 mL (odds ratio [OR], 3.666; 95% confidence interval [CI], 1.407–9.550; $p=0.008$), CRE rectal carriage within 30 days post-LT (OR, 5.516; 95% CI, 2.113–14.399; $p=0.000$), biliary complications (OR, 3.779; 95% CI, 1.033–13.831; $p=0.045$) and renal replacement therapy for more than 3 days (OR, 3.762; 95% CI, 1.196–11.833; $p=0.023$) were independent risk factors for CRE infections within 30 days post-LT.

Conclusion: CRE infections within 30 days post-LT were associated with worse outcomes. Intraoperative blood loss equal to or more than 1500 mL, CRE rectal carriage within 30 days post-LT, biliary complications and renal replacement therapy for more than 3 days were independent risk factors of CRE infections after LT.

Keywords: carbapenem-resistant Enterobacteriaceae, liver transplantation, infections, immunosuppression, mortality, risk factors

Introduction

Infectious complications are major causes of morbidity and mortality after liver transplantation. Over the past decade, the emergence of carbapenem-resistant Enterobacteriaceae (CRE) has become a serious healthcare problem worldwide. CRE infections are associated with worse outcomes among liver transplant (LT) recipients.[1] Such infections occur most often in the early post-transplant period, the median time from LT to CRE infection ranging from 12 to 24 days.[1–3]

In view of the poor prognosis of CRE infection among LT recipients, improved understanding about its risk factors is crucial for the development of effective

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prevention strategies. There are few studies about the risk factors of post-transplant CRE infections, which include high Model for End-Stage Liver Disease (MELD) score, CRE colonization, dialysis after LT, prolonged mechanical ventilation time, hepatitis C virus (HCV) recurrence, reintervention and rejection.[4–6] However, the risk factors for CRE infection differ between the periods after transplantation, and between centers. To prevent post-LT CRE infections, proper strategies should be based on more center-specific data and evidence from well-controlled clinical studies.

The aim of this study was to analyze the risk factors and outcomes for CRE infections within the first 30 days after LT in a Chinese population.

Patients and Methods

Study Design and Participants

This study involved all adult patients (age >18 years) who had their first liver-only transplant, with no evidence of pre-transplant CRE infection, between December 2017 and September 2019 at the Frist Affiliated Hospital of Zhejiang University, School of Medicine, China. Patients were followed from hospital admission until October 31st, 2019. Perioperative antibacterial prophylaxis was given for at least 72 h post-transplantation. The immunosuppression consisted of induction with basiliximab and corticosteroid, then maintenance with tacrolimus and mycophenolate mofetil, with or without corticosteroid for the early stage post-LT.

Setting

The Frist Affiliated Hospital of Zhejiang University, School of Medicine, is a 2200-bed tertiary care University Hospital in Hangzhou, China. Our liver transplant center has performed 2806 liver transplantations up to December 2019.

Data Collection and Definitions

Variables were collected on patients' electronic case reports. The variables evaluated in this study included: recipients' condition (age, sex, body mass index [BMI], MELD score, Child–Pugh score, underlying liver diseases, pre-LT intensive care unit [ICU] stay); graft information (graft type, cold ischemia time, hot ischemia time), procedure-related information (intraoperative blood loss, vascular complications, biliary complications, reoperation), CRE rectal carriage status in the first month post-transplant, post-transplant conditions (mechanical ventilation, renal replacement therapy), CRE infection variables (time, location, pathogen, concurrent infections) and outcomes (30-day and 180-day survival rates).

CRE is defined as Enterobacteriaceae that is resistant to at least one of the carbapenem antibiotics (ertapenem, meropenem, doripenem or imipenem) or produces a carbapenemase according to the Centers for Disease Control and Prevention.[7] Detection of carbapenem resistance is based on Clinical and Laboratory Standards Institute (CLSI) breakpoints.[8] All paitents were screened for CRE carriage when they arrived in the ICU after liver transplantation. Two consequent CRE swabs were performed on the day and 1 day post-LT. The CRE swab was repeated at 3–5-day intervals thereafter until the patient was transferred to the general ward. CRE carriage was defined as the isolation of CRE from a rectal swab in the absence of symptoms and signs of invasive infection.

Infection was identified using a combination of imaging, clinical and laboratory criteria, as outlined by CDC/NHSN 2019.[9] However, since this was a retrospective study and focused on CRE infection, we only included culture-positive infections in this study. Patients with positive CRE culture from blood, peritoneal fluid, biliary juice, sputum, endotracheal aspiration, urine and others according to the CDC/NHSN criteria were evaluated retrospectively to assess whether patients had CRE infections based on two experts' opinions.

Vascular complications included hepatic artery thrombosis, hepatic vein thrombosis and portal vein thrombosis. Biliary complications included bile duct stenosis and bile leakage.

Statistical Analysis

Patients who developed CRE infections within 30 days after LT were compared with those without CRE infections. Continuous variables were compared using Student's t or Mann–Whitney U-test. Categorical variables were compared using Pearson chi-square or Fisher's exact test when appropriate. All variables with a p-value <0.05 in the univariate analysis were entered into the logistic regression for multivariable analysis. A Kaplan–Meier analysis was performed to determine the survival rate between the two groups. A p value <0.05 was considered statistically significant. All statistical calculations were performed with SPSS 25.

Results

Characteristics of CRE Infections

This study consisted of 387 patients who underwent their first liver-only transplantation. Among them, 26 patients

(6.7%) developed CRE infections within a median of 7.5 (interquartile range [IQR] 3.5–13.25) days after LT. The basic characteristics of patients with and those without CRE infections are shown in Table 1. Compared with patients without CRE infections, those with CRE infections had similar pre-LT conditions (age, sex, BMI, Child–Pugh score, pre-LT ICU stay), except that they had higher MELD score (25.23±11.22 vs 19.74±9.86, p=0.007) and were more likely to have alcoholic liver disease as the primary liver disease (15.4% vs 4.7%, p=0.020). Regarding graft conditions (graft type, cold ischemia time, hot ischemia time), there was no significant difference detected between patients with and those without CRE infections. For post-transplant conditions, patients with CRE infections were more likely to have vascular complications (11.5% vs 1.4%, p=0.000), biliary complications (19.2% vs 6.6%, p=0.019), reoperation (30.8% vs 5.3%, p=0.000), mechanical ventilation for more than 72 h (30.8% vs 6.9%, p=0.000) and renal replacement therapy for more than 3 days (38.5% vs 10.0%, p=0.000).

Among the 26 patients with CRE infections, 24 patients (92.3%) had carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections, one patient (3.8%) had carbapenem-resistant *Enterobacter cloacae* infection and one patient (3.8%) had carbapenem-resistant *Enterobacter aerogenes* infection. It was not uncommon for patients to have more than one location of infection: 21 patients (80.8%) had intra-abdominal infections, 16 patients (61.5%) developed CRE bacteremia and six patients (16.7%) had pneumonia. Moreover, 15 patients (57.7%) had other concurrent bacterial infections, such as *Enterococcus faecium* or *Acinetobacter baumannii*.

CRE Rectal Carriage

CRE rectal carriage was detected in 65 patients out of 387 (16.8%). Patients developed CRE rectal carriage within a median of 5 (IQR 4–8.5) days after LT. Among them, eight patients had positive CRE rectal carriage within 48 h post-LT. It was difficult for us to tell whether those eight patients had acquired CRE colonization before or after LT, because our center did not routinely screen for CRE rectal carriage before LT. Thirteen out of the 65 patients (20%) with CRE rectal carriage eventually developed CRE infections. Eleven patients had the same pathogen (CRKP) of both infection and rectal carriage. One patient had carbapenem-resistant *E. aerogenes* rectal carriage but CRKP infection. Another had CRKP carriage but carbapenem-resistant *E. cloacae* infection.

Risk Factors for CRE Infections

Univariate analysis suggested that nine factors, namely MELD score, alcoholic liver disease, intraoperative blood loss ≥1500 mL, CRE rectal carriage at any time within 30 days post-LT, ventilation for >72 h, reoperation, biliary complications, vascular complications and renal replacement therapy for >3 days were associated with post-LT CRE infections (Table 1). Multivariate analysis identified that intraoperative blood loss ≥1500 mL (OR, 3.666; 95% CI, 1.407–9.550; p=0.008), CRE rectal carriage within 30 days post-LT (OR, 5.516; 95% CI, 2.113–14.399; p=0.000), biliary complications (OR, 3.779; 95% CI, 1.-033–13.831; p=0.045) and renal replacement therapy for >3 days (OR, 3.762; 95% CI, 1.196–11.833; p=0.023) were independent risk factors for CRE infections (Table 2).

Post-LT Outcomes

Patients with post-LT CRE infections had significantly lower 30-day and 180-day survival rates than those without (80.8% vs 96.4%, p<0.001; 51.5% vs 92.4%, p<0.001). To further show the severity of CRE infections, we also compared survival rates between patients with CRE bloodstream infections (n=16) and those with other pathogen bloodstream infections (n=47) occurring within 30 days post-LT, and found that those with CRE bloodstream infections had much lower 30-day and 180-day survival rates (75.0% vs 95.7%, p<0.001; 41.0% vs 91.4%, p<0.001) (Figure 1).

Discussion

According to the China Antimicrobial Surveillance Network (CHINET) 2018 report, the resistance rates of *K. pneumoniae* to imipenem and meropenem had increased to 25% and 26.3%, respectively, in 2018, from 3.0% and 2.9% in 2005, and the resistance rate increased more than eight times.[10] The rapid increase in CRE has posed great challenges for the management of LT patients. To the best of our knowledge, this is the first study specifically describing the risk factors and outcomes associated with CRE infections within 30 days after liver transplantation in a Chinese population. The incidence of post-LT CRE infection varies among different centers, from 3% to 23%.[2,5,11] In our center, the incidence of CRE infection was 6.7% in the first 30 days after LT, and the majority of them had CRKP infections. CRE infections were related to high mortality among transplant patients. One study

Table 1 Comparison of Patients with and without CRE Infection Within 30 Days After Liver Transplantation

	Patients with CRE Infection, n=26 (6.7%)	Patients without CRE Infection, n=361 (93.3%)	*p*
Age (years), median±SD)	48.6 2±11.29	50.65±10.21	0.330
Sex, male	22 (84.6%)	279 (77.3%)	0.472
BMI (kg/m^2)	28.12±9.25	26.59±9.32	0.419
MELD, median±SD)	25.23±11.22	19.74±9.86	0.007
Child-Pugh score	9.88±2.37	9.26±2.58	0.229
Pre-LT ICU stay	6 (23.1%)	38 (10.5%)	0.052
Underlying liver disease[a]			
HBV	18 (69.2%)	283 (78.4%)	0.278
HCC	7 (26.9%)	121 (33.5%)	0.490
Alcohol	4 (15.4%)	17 (4.7%)	0.020
AIH	1 (3.8%)	21 (5.8%)	0.675
PBC	0	1 (0.3%)	0.548
Others	2 (7.7%)	42 (11.6%)	0.541
Graft type			0.959
DBCD	4 (15.4%)	49 (13.6%)	
DBD	6 (23.1%)	89 (24.6%)	
DCD	16 (61.5%)	223 (61.8%)	
Living donor	0	0	
Cold ischemia time (min), median±SD)	590.26±162.39	550.26±180.99	0.305
Hot ischemia time (min), median±SD)	10.95±7.00	10.23±8.24	0.696
Intraoperative bleeding ≥1500 mL	14 (53.8%)	91 (25.2%)	0.002
CRE rectal carriage within 30 days post-LT	13 (50.0%)	52 (14.4%)	0.000
Vascular complications	3 (11.5%)	5 (1.4%)	0.000
Biliary complications	5 (19.2%)	24 (6.6%)	0.019
Reoperation	8 (30.8%)	19 (5.3%)	0.000
Ventilated >72 h	8 (30.8%)	25 (6.9%)	0.000
Renal replacement therapy >3 days	10 (38.5%)	36 (10.0%)	0.000

Note: [a]Some patient presented more than one cause of liver disease.

Abbreviations: AIH, autoimmune hepatitis; BMI, body mass index; CRE, carbapenem-resistant Enterobacteriaceae; DBD, donation after brain death; DBCD, donation after brain death followed by circulatory death; DCD, donation after circulatory death; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; PBC, primary biliary cirrhosis; pre-LT ICU stay, pre-liver transplantation intensive care unit stay; SD, standard deviation.

Table 2 Multivariate Analysis of Risk Factors for CRE Infection After Liver Transplantation

	OR	95% CI	*p*
MELD	1.006	0.950–1.065	0.842
Alcoholic liver disease	4.094	0.910–18.415	0.066
Intraoperative bleeding ≥1500 mL	3.666	1.407–9.550	0.008
CRE rectal carriage within 30 days post-LT	5.516	2.113–14.399	0.000
Ventilated >72 h	2.344	0.636–8.639	0.201
Reoperation	2.673	0.773–9.244	0.121
Biliary complications	3.779	1.033–13.831	0.045
Vascular complications	5.357	0.690–41.600	0.109
Renal replacement therapy >3 days	3.762	1.196–11.833	0.023

Abbreviations: CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; OR, odds ratio.

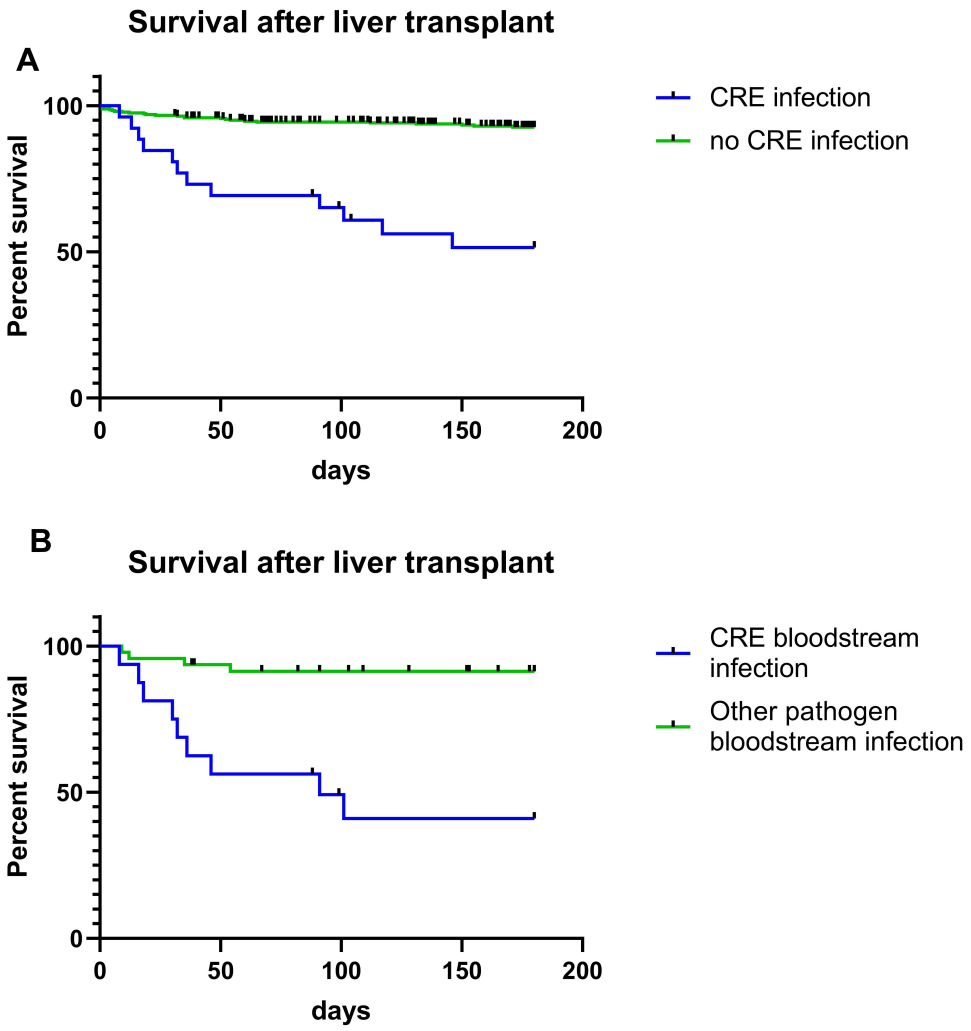

Figure 1 Survival rates associated with carbapenem-resistant Enterobacteriaceae (CRE) infections. (**A**) A Kaplan–Meier analysis demonstrated reduced 180-day survival for liver transplant (LT) recipients with CRE infections versus LT recipients without CRE infections (51.5% vs 92.4%, log-rank $p<0.001$). (**B**) A Kaplan–Meier analysis demonstrated reduced 180-day survival for LT recipients with CRE bloodstream infections versus LT recipients with other pathogen bloodstream infections (41.0% vs 91.4%, log-rank $p<0.001$).

showed that the mortality rate for LT patients with CRKP infections was 78%, compared to 32% for carbapenem-susceptible *K. pneumoniae* infections.[3] In our center, the 180-day survival rate dropped from 92.4% to 51.5% with CRE infections. Moreover, compared to patients with post-LT CRE bacteremia, those with other pathogen bloodstream infections also had much better outcomes.

A few factors may contribute to the high mortality rate of CRE infections. Firstly, CRE infections tend to attack the most vulnerable LT patients, who had worse underlying conditions, went through complicated surgical procedures or suffered from surgical or medical complications.[3–6,12] In our center, CRE infections tend to occur in patients with worse pre- or post-LT conditions, high MELD score, high intraoperative blood loss, reoperation, biliary complications, vascular complications, prolonged ventilation time or prolonged renal replacement therapy, as shown in Table 1. Secondly, identification of CRE from clinical specimens can take up to 2–3 days; therefore, the administration of appropriate therapy can be delayed.[11] Also, effective antimicrobial agents, such as polymyxins, aminoglycosides, fosfomycin and tigecycline, carry a high risk of toxicity and/or suboptimal efficacy.[13]

In this study, we found that the most common types of CRE infections within first 30 days post-LT were intra-abdominal infections and bloodstream infections. In addition, the risk factors for CRE infections are related to surgical procedures or medical complications, including high intraoperative blood loss, biliary complications and prolonged renal replacement therapy. As previous studies

showed, the risk factors and patterns of bacterial infection change along the post-transplant time course and they are commonly divided into three phases: the first month, the second to sixth months, and more than six months after transplantation.[14] In the first month after LT, most infections are related to the surgical procedures and medical complications.[14,15] Surgical site infections (SSIs), including deep intra-abdominal infections, pneumonia, bacteremia, urinary tract infections and catheter-related infections, are common early after LT.[16–19] From Table 2, we also noticed that 29.6% of patients who underwent reoperation, 17.2% of patients who had biliary complications and 37.5% of patients who had vascular complications eventually had CRE infection within 30 days post-LT. Since it is not unusual for post-LT infections to have an atypical presentation, and inappropriate antimicrobial treatment is associated with worse outcome, active screening for CRE infections in those patients with surgical complications may help in early detection and early initiation of proper antibiotics.[13,20] However, strategies such as empiric use of CRE-active therapy in high-risk patients are still inconclusive, because it may contribute to the further emergence of multi-drug resistant (MDR) infections and/or adverse effects in patients.[13]

CRE colonization has been reported to be associated with a higher risk of CRE infections and worse outcomes.[3–6] In our study, we also noticed that CRE rectal carriage at any time within 30 days post-LT is an independent risk factor for developing post-LT CRE infections. Oral colistin or gentamicin has been used for CRE intestinal decolonization.[21,22] However, it remains inconclusive whether CRE decolonization can prevent CRE infections or improve outcomes in LT patients. ESCMID-EUCIC clinical guidelines do not recommend routine decolonization of CRE in immunocompetent patients.[23] But for solid organ transplant recipients, clinical evidence is limited. Also, no study has specifically addressed the surgical prophylaxis regimens in patients colonized with CRE. In view of the limited clinical evidence, intestinal decolonization and using different surgical prophylaxis are not yet recommended for LT patients with CRE colonization.[24] However, we believe that CRE screening should still be performed both before and after transplantation, even through no pharmacological interventions are recommended at present. Apart from reinforcing infection-control strategies such as hand hygiene and contact precautions to prevent CRE transmission in hospital, positive CRE screening will provide clinicians with valuable information when they face septic transplant patients with unknown pathogens. Furthermore, good clinical trials are needed to guide the future management of transplant patients.

Our study has some limitations. Firstly, it was a monocentric retrospective study. Our data may vary from other centers. However, the incidence, source and survival rate of CRE infections observed in our cohort are similar to those described by other studies. Another limitation was the lack of information about CRE colonization prior to LT, because we did not screen all LT candidates before LT.

Conclusion

We found that CRE infections occurring within 30 days after liver transplantation were associated with worse outcomes. Intraoperative blood loss equal to or more than 1500 mL, CRE rectal carriage within 30 days post-LT, biliary complications and renal replacement therapy for more than 3 days were independent risk factors for CRE infections. In the view of poor outcomes of CRE infections, prevention is perhaps one of the most important strategies for decreasing the morbidity and mortality associated with CRE infections. High-quality studies are needed to build a proper risk-stratification system to help guide the early initiation of CRE active antibiotics to treat high-risk LT patients, and at the same time to limit the empiric overuse of antibiotics in low-risk patients.

Ethical Approval

This study complied with the guidelines of the Chinese Ethics Committee and the Declaration of Helsinki, and was approved by research ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine. All organs were donated voluntarily with written informed consent, and the organ donations were conducted in accordance with the Declaration of Istanbul. Patients were not required to give informed consent to this study because the analysis used anonymous data.

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Disclosure

The authors report no conflicts of interest for this work and declare that there is no competing interest regarding the publication of this paper.

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