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Bacterial and Fungal Infections After Liver Transplantation: Microbial Epidemiology, Risk Factors for Infection and Death with Infection

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Background: Infections, especially bacterial and fungal infections, are the leading cause of high mortality after liver transplantation (LT). This research investigated the pathogenic spectrum, antimicrobial susceptibility results, and risk factors of infection and death with infection to better control such infections.

Material/Methods: A retrospective cohort study was performed, and 433 liver transplant recipients between January 2010 and December 2016 were analyzed.

Results: We found 290 isolates of bacteria and fungi in 170 infected liver transplant patients. Significant independent risk factors for bacterial and fungal infections were prolonged hospital stay (OR 1.034, 95% CI 1.013~1.056, $p=0.002$), mechanical ventilation (OR 3.806, 95% CI 1.567~9.248, $p=0.003$), and liver failure (OR 2.659, 95% CI 1.019~6.940, $p=0.046$). Furthermore, postoperative MELD scores (OR 1.120, 95% CI 1.020~1.230, $p=0.017$) and septic shock (OR 12.000, 95% CI 1.124~128.066, $p=0.003$) were independent risk factors for death with infection. CRAB infection is the main pathogenic bacteria of septic shock in LT patients.

Conclusions: We found that 39.3% of recipients had at least 1 bacterial or fungal infection after LT. Shortening the length of hospital stay and early withdrawal of mechanical ventilation will reduce the risk of infection after LT. Patients with liver failure should be more vigilant against postoperative infection. Once an infection occurs, immediate assessment of the postoperative MELD score, early diagnosis of septic shock, and active search for pathogenic evidence for precise treatment will help improve patient prognosis. Routine screening for CRAB colonization before surgery will facilitate empirical use of effective antibiotics.

MeSH Keywords: Bacterial Infections • Liver Transplantation • Risk Factors

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Background

Liver transplantation (LT) is an effective treatment for end-stage liver diseases. With the improvement of surgical techniques, post-LT management of complications, and the use of new immunosuppressive regimens, recipient survival after LT has increased steadily, with a current 5-year survival rate of between 70% and 80% [1,2]. However, the use of immunosuppressants also increases the risk of infection, leading to high mortality. In Europe, 18% of post-LT deaths are caused by infection [2]. The majority of infections are caused by bacteria (70%), followed by virus (10%) and fungus (8%) [3,4].

With the use of antibiotics, hospital-acquired infections are rising recently, especially multi-drug-resistant bacteria such as carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant Enterobacteriaceae (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE). For LT recipients with immunosuppressive state, MDR infection can be fatal [5–9]. At the same time, LT recipients are admitted to the intensive care unit after surgery. The operation itself and frequent invasive procedures increase the possibility of infection in transplant patients. Therefore, the primary purpose of our study was to assess the pathogenic spectrum and antimicrobial susceptibility results to administer appropriate antibiotics and avoid drug resistance in clinical practice. We also identify the risk factors for infection and death with infection to prevent infection and reduce the incidence of death related to infection.

Material and Methods

Study design and recipients

We conducted a retrospective cohort study that included all adult (age ≥ 18 years) patients undergoing LT at West China Hospital, from January 2010 to December 2016. The patients without regular outpatient follow-up were excluded. For the included patients, if infection occurred, they were often admitted to the hospital for treatment. In total, 433 recipients (358 males and 75 females) were included. The mean age was 47 years (range, 18–79 years). The study group consisted of those recipients who developed at least 1 bacterial or fungal infection within 1 year after LT. Demographic, microbiological, and clinical characteristics were assessed. This study was approved by the hospital Ethics Committee and was performed in accordance with the Declaration of Helsinki [10].

Data

All patients were reviewed for the detection of bacterial and fungal infections after LT, including the sites and period of

infection, culture outcomes, and antimicrobial susceptibility results. Potential risk factors for bacterial or fungal infection and death with infection were collected after LT, including demographic data (sex and age); reasons for LT; time of hospitalization after LT; laboratory index, including prothrombin time (PT) and international normalized ratio (INR); and serum bilirubin, serum creatinine, and albumin. Scores of model for end-stage liver disease (MELD) were calculated.

Immunosuppressive and rejection therapy

All LT patients received primary standard immunosuppressive therapy, including tacrolimus (FK506) or cyclosporine combined with mycophenolate mofetil (MMF) and low-dose prednisone. Methylprednisolone was started intraoperatively (10 mg/kg/dose) and continued with tapering for the first 3 months after LT. The target level of tacrolimus was 8–12 ng/ml in the first 3 months, 7–10 ng/ml in 3–6 months, 6–8 ng/ml in 6–12 months, and < 5 ng/ml after the first year. For cyclosporine, the target levels of peak concentration were 900–1100 ng/ml in the first 3 months, 800–1000 ng/ml in 3–6 months, 600–800 ng/ml in 6–12 months, and < 500 ng/ml after the first year. Prednisolone was administered at a dose of 10 mg and gradually decreased to zero in the first 3 months. The onset of acute rejection was diagnosed by the patient's clinical manifestations, laboratory medical tests, and liver biopsy. Rejection was mainly treated with methylprednisolone (3 mg/kg/day for 5 days) and increasing FK506 blood concentrations.

Definition and microbiology

Infections included bacterial and fungal infections. The definition of urinary tract infection (UTI) was: $> 10^5$ CFU/ml plus at least one of the following clinical signs: a. fever; b. functional urinary symptoms; and c. sepsis of unknown origin. The definition of pneumonia was: isolated pathogen from sputum or bronchoalveolar lavage fluid (BALF) plus at least 3 of the following clinical signs: a. radiological signs; b. fever; c. white blood cell (WBC) count < 4000 cells/mm³ or $> 12\,000$ cells/mm³; d. cough; e. purulent pulmonary secretions or change in odor, consistency, color, or quantity; and f. dyspnea, tachypnea, apnea, or grunting. The definition of blood stream infection (BSI) was: isolated pathogen from 1 or more percutaneous blood cultures plus fever, chills, or hypotension. The definition of spontaneous bacterial peritonitis (SBP) was: ascitic fluid culture positivity (bacterascites) and/or an ascitic fluid polymorphonuclear leucocyte count greater than 250/mm³ ($0.25 \times 10^9/L$). The definition of septic shock [11] was: at least 2 of the following clinical signs: a. body temperature $> 38.0^\circ\text{C}$ or $< 36.0^\circ\text{C}$; heart rate > 90 beats/min; c. tachypnea > 20 breaths/min or hyperventilation with PaCO₂ < 32 mmHg; d. WBC count $> 12\,000$ cells/mm³; or < 4000 cells/mm³. Death with infection was defined as all-cause death in the perioperative period in infected patients after LT.

The microorganisms were cultured and identified according to standard operating procedures of various samples, including sputum, blood, urine, ascites, and bile. Susceptibility tests of the strains to antibacterial agents were performed by standard methods, and the patterns were reviewed and classified according to the CLSI (Clinical and Laboratory Standards Institute) guidelines.

Statistical analysis

Statistical analysis was performed using SPSS software, version 20 (SPSS, Inc., Chicago, IL). Categorical variables are expressed as absolute numbers and their relative frequencies. Continuous variables are expressed as mean±standard deviation (SD) if normally distributed, or as the median and interquartile range (IQR) if non-normally distributed. Patients who developed at least 1 bacterial or fungal infection within after LT were compared with those without infection during this period. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the *t* test or Mann-Whitney U test, according to their distribution. The significant risk factors identified in univariate analysis ($P<0.05$) were included in multivariate analysis. For multivariate analysis, logistic regression models with stepwise variable selection were used to determine risk factors for infection. $P<0.05$ was considered statistically significant.

Results

Recipients characteristics

Among 433 LT recipients considered in the study period, 170 (39.3%) had at least 1 infection documented within a median of 20 days (IQR 9–73) after LT. The median age was 47 years old and males accounted for 82.7% (358/433) of the population. The majority of the patients underwent LT due to liver cancer ($n=217$), including hepatitis B-related liver cancer ($n=140$) and other liver cancer ($n=77$), due to the following: liver cirrhosis ($n=149$), including hepatitis B-related cirrhosis ($n=75$), hepatitis C-related cirrhosis ($n=6$), alcoholic liver cirrhosis ($n=14$), cholestasis ($n=13$), primary biliary cirrhosis ($n=5$), autoimmune hepatitis ($n=3$), re-transplantation ($n=4$), Wilson's disease ($n=3$), citrin deficiency disease ($n=3$), schistosomiasis liver cirrhosis ($n=1$), mixed cirrhosis ($n=2$), and other liver cirrhosis ($n=20$). The remaining cases involved liver failure ($n=67$), including hepatitis B-related liver failure ($n=48$) and other liver failure ($n=19$) (Table 1).

Table 1. Recipients' demographic and characteristics.

n=433	
Age ^a (year)	47 (42–54)
Gender ^b	
Male	358 (82.7)
Female	75 (17.3)
Hospital stay (days)	23.5 (17.0–34.0)
Years of transplantation ^b	
2010	62 (14.3)
2011	51 (11.8)
2012	43 (10.0)
2013	55 (12.7)
2014	61 (14.1)
2015	58 (13.4)
2016	103 (23.8)
Reasons for liver transplantation ^b	
Liver cancer	
Hepatitis B-related	140 (32.3)
Others	77 (17.8)
Liver cirrhosis	
HBV	75 (17.3)
HCV	6 (1.4)
Alcoholic liver cirrhosis	14 (3.2)
Cholestasis	13 (3.0)
Primary biliary cirrhosis	5 (1.2)
Autoimmune hepatitis	3 (0.7)
Re-transplantation	4 (0.9)
Wilson's disease	3 (0.7)
Citrin deficiency disease	3 (0.7)
Schistosomiasis liver cirrhosis	1 (0.2)
Mixed	2 (0.5)
Others	20 (4.6)
Liver failure	
Hepatitis B-related	48 (11.1)
Others	19 (4.4)

^a Continuous data was presented by median with interquartile range (IQR); ^b categorical data was presented by count and percentage. HBV – hepatitis B virus; HCV – hepatitis C virus.

Pathogenic spectrum

We detected 290 episodes of bacterial or fungal infection in our study. Gram-positive bacteria, gram-negative bacteria, and fungi accounted for 20.0% (58/290), 67.9% (197/290), and 12.1% (35/290) of pathogens, respectively. The most common gram-negative bacteria were *Acinetobacter baumannii* (26.6%), *Klebsiella pneumoniae* (14.1%), *Pseudomonas aeruginosa* (7.9%), *Escherichia coli* (6.2%), and *Stenotrophomonas maltophilia* (3.1%). The most common gram-positive bacteria were *Enterococcus faecium* (13.1%), *Staphylococcus aureus* (2.0%), and coagulase-negative *Staphylococcus* (1.7%). The fungal infections were mainly *Candida* (10.3%), *Aspergillus* (1.0%), and *Cryptococcus* (0.3%) (Table 2).

In total, pneumonia (53.1%) and bloodstream infections (13.8%) were the most common infections. Pneumonia were mainly caused by *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Candida*. Bloodstream infections were mainly caused by *Enterococcus faecium*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*.

We also compared the pathogenic spectrum of different MELD score groups. When MELD scores were less than 15, the most common pathogens were *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Enterococcus faecium*, and *Candida*. When MELD scores were between 15 and 30, the most common pathogens were *Acinetobacter baumannii*, *Enterococcus faecium*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. In the group with MELD scores over 30, 8 strains were isolated (Table 3).

Antimicrobial susceptibility results

As shown in Table 4, 67.6% *Klebsiella pneumoniae* isolates and 77.8% *Escherichia coli* isolates produced ESBLs. For *Klebsiella pneumoniae*, the antibiotic with less than 10% resistance rate was polymyxin B; antibiotics with resistance rates between 10% and 20% were amikacin, cefotetan, carbapenems, piperacillin/tazobactam, and tigecycline. For *Escherichia coli*, antibiotics with resistance rates less than 10% were amikacin, cefotetan, nitrofurantoin, and carbapenems. For *Pseudomonas aeruginosa*, the resistance rate of amikacin was less than 25%, and for *Acinetobacter baumannii*, only polymyxin B and tigecycline were less than 25% (Table 4).

Risk factors for infection

A comparison of patients with and without infection is shown in Table 5. Age, female patients, hospital stay, liver failure, and postoperative MELD scores, blood loss during operation, transfusions of packed RBC, transfusion FFP, and mechanical ventilation, urinary catheterization, and arteriovenous catheterization

were identified as risk factors of infection. In contrast, the prevalence of liver cancer in the infection group (36.5%) was lower than that in the non-infection group (58.9%) (Table 5).

Multivariate analysis revealed that independent risk factors for infection recipients were prolonged hospital stay (OR 1.034, 95% CI 1.013–1.056, $p=0.002$), liver failure (OR 2.659, 95% CI 1.019–6.940, $p=0.046$), and mechanical ventilation (OR 3.806, 95% CI 1.567–9.248, $p=0.003$) (Table 4).

Risk factors for death with infection

The 170 infected patients were divided into a death group ($n=26$) and a survival group ($n=144$) according to whether perioperative death occurred. When we compared the 2 groups, we found that female sex, postoperative MELD scores, septic shock, multi-site infection, blood loss during operation, transfusions of packed RBC, and prolonged mechanical ventilation were risk factors for death with infection (Table 6).

Multivariate analysis revealed postoperative MELD scores (OR 1.120, 95% CI 1.020–1.230, $p=0.017$) and septic shock (OR 12.000, 95% CI 1.124–128.066, $p=0.003$) as independent risk factors for death with infection (Table 6).

Septic shock

Table 7 lists the clinical data of 16 patients with septic shock in the death with infection group, including 10 males and 6 females, whose median of age was 48.5 years (IQR 45–57.5) and the median of MELD score was 19 (IQR 10–25). Carbapenem-resistant *Acinetobacter baumannii* (CRAB) was isolated in 13 cases (81.25%) and *Enterococcus faecium* was isolated in 5 cases (31.25%).

Discussion

Bacterial and fungal infections are among the leading causes of death after LT. The present study assessed the clinical characteristics of patients with LT and analyzed the data on pathogenic microorganisms and antibacterial treatments to provide theoretical evidence for the prevention and treatment of infection after LT and to reduce the mortality rate of LT patients. Our research found that pathogenic bacteria isolated from LT patients generally have high resistance to antibiotics. Especially in patients with septic shock, the proportion of CRAB was very high, but the empirical antibiotic treatment was often ineffective. Furthermore, the analysis of the clinical characteristics of patients found that liver failure, but not MELD scores, could predict the risk of infection in LT patients. However, MELD scores and septic shock could predict the risk of death in the infected patients.

Table 2. The spectrum of infection sites.

	Respiratory tract	Blood stream	Abdomen	Urine tract	Bile tract	Multiple sites	Other sites	n=290
Gram-negative bacteria	126 (64.0)	20 (10.2)	12 (6.1)	5 (2.5)	10 (5.1)	12 (6.1)	12 (6.1)	197 (67.9)
<i>Acinetobacter baumannii</i>	52	5	6	2	3	8	1	77 (26.6)
<i>Klebsiella pneumonia</i>	24	7	2	0	1	2	5	41 (14.1)
<i>Klebsiella oxytoca</i>	4	0	0	0	2	0	0	6 (2.1)
<i>Pseudomonas aeruginosa</i>	16	1	1	1	2	0	2	23 (7.9)
<i>Pseudomonas paucimobilis</i>	1	0	0	0	0	0	0	1 (0.3)
<i>Escherichia coli</i>	8	1	3	2	0	2	2	18 (6.2)
<i>Stenotrophomonas maltophilia</i>	8	1	0	0	0	0	0	9 (3.1)
<i>Burkholderia cepacia</i>	4	1	0	0	0	0	0	5 (0.3)
<i>Burkholderia pickettii</i>	0	1	0	0	0	0	0	1 (0.3)
<i>Enterobacter cloacae</i>	3	1	0	0	0	0	0	4 (1.4)
<i>Enterobacter aerogenes</i>	2	0	0	0	0	0	0	2 (0.7)
<i>Citrobacter</i>	0	1	0	0	1	0	1	3 (1.0)
<i>Morgan morganella</i>	0	0	0	0	0	0	1	1 (0.3)
<i>Hafnia alveibifementans</i>	1	0	0	0	0	0	0	1 (0.3)
<i>Proteus mirabilis</i>	0	0	0	0	1	0	0	1 (0.3)
<i>Ochrobactrum anthropi</i>	1	0	0	0	0	0	0	1 (0.3)
<i>Aeromonas hydrophila</i>	1	0	0	0	0	0	0	1 (0.3)
<i>Serratia liquefaciens</i>	1	0	0	0	0	0	0	1 (0.3)
<i>Serratia marcescens</i>	0	1	0	0	0	0	0	1 (0.3)
Gram-positive bacteria	3 (5.2)	18 (31.0)	11 (19.0)	8 (13.8)	4 (6.9)	8 (13.8)	6 (10.3)	58 (20.0)
<i>Enterococcus faecium</i>	0	10	8	7	3	7	3	38 (13.1)
<i>Enterococcus faecalis</i>	0	0	0	1	0	0	1	2 (0.7)
<i>Enterococcus gallinarum</i>	0	2	0	0	0	0	0	2 (0.7)
<i>Staphylococcus aureus</i>	2	2	1	0	0	1	0	6 (2.0)
Coagulase-negative <i>Staphylococcus</i>	0	2	1	0	1	0	1	5 (1.7)
<i>Streptococcus pneumoniae</i>	0	1	0	0	0	0	0	1 (0.3)
<i>Streptococcus oralis</i>	1	0	0	0	0	0	0	1 (0.3)
Group G <i>Streptococcus</i>	0	0	0	0	0	0	1	1 (0.3)
Non-group A/B/D <i>Streptococcus</i>	0	0	1	0	0	0	0	1 (0.3)
<i>Leuconostoc pseudomesenteroides</i>	0	1	0	0	0	0	0	1 (0.3)
Fungus	25 (71.4)	2 (5.7)	4 (11.4)	2 (5.7)	0 (0)	0 (0)	2 (5.7)	35 (12.1)
<i>Candida</i>	22	1	4	2	0	0	2	31 (10.3)
<i>Aspergillus</i>	3	0	0	0	0	0	0	3 (1.0)
<i>Cryptococcus</i>	0	1	0	0	0	0	0	1 (0.3)
Total	154 (53.1)	40 (13.8)	27 (9.3)	15 (5.2)	14 (4.8)	20 (6.9)	20 (6.9)	290(100)

Table 3. The pathogenic spectrum of different MELD score groups.

	MELD score <15 (n=130)	15 ≤ MELD score ≤30 (n=33)	MELD score >30 (n=7)
Gram-negative bacteria			
<i>Acinetobacter baumannii</i>	50	25	2
<i>Klebsiella pneumonia</i>	33	8	0
<i>Klebsiella oxytoca</i>	5	1	0
<i>Pseudomonas aeruginosa</i>	12	9	2
<i>Pseudomonas paucimobilis</i>	1	0	0
<i>Escherichia coli</i>	14	4	0
<i>Stenotrophomonas maltophilia</i>	6	3	0
<i>Burkholderia cepacia</i>	3	2	0
<i>Burkholderia pickettii</i>	1	0	0
<i>Enterobacter cloacae</i>	3	1	0
<i>Enterobacter aerogenes</i>	2	0	0
<i>Citrobacter</i>	3	0	0
<i>Morgan morganella</i>	1	0	0
<i>Hafnia alveibifementans</i>	0	0	1
<i>Proteus mirabilis</i>	1	0	0
<i>Ochrobactrum anthropi</i>	1	0	0
<i>Aeromonas hydrophila</i>	1	0	0
<i>Serratia liquefaciens</i>	1	0	0
<i>Serratia marcescens</i>	1	0	0
Gram-positive bacteria			
<i>Enterococcus faecium</i>	26	10	2
<i>Enterococcus faecalis</i>	2	0	0
<i>Enterococcus gallinarum</i>	2	0	0
<i>Staphylococcus aureus</i>	3	2	1
Coagulase-negative <i>Staphylococcus</i>	5	0	0
<i>Streptococcus pneumoniae</i>	1	0	0
<i>Streptococcus oralis</i>	0	1	0
Group G <i>Streptococcus</i>	0	1	0
Non-group A/B/D <i>Streptococcus</i>	1	0	0
<i>Leuconostoc pseudomesenteroides</i>	1	0	0
Fungus			
<i>Candida spp.</i>	26	5	0
<i>Aspergillus spp.</i>	2	1	0
<i>Cryptococcus spp.</i>	1	0	0

Table 4. The resistance rates to antimicrobial agents.

	<i>Acinetobacter baumannii</i> (n=77)		<i>Escherichia coli</i> (n=18)		<i>Klebsiella pneumoniae</i> (n=41)		<i>Pseudomonas aeruginosa</i> (n=23)	
Ampicillin	N/A ^b		93.8	(15/16)	N/A ^b		N/A ^b	
Cefoxitin	N/A ^b		50.0 ^a	(1/2)	26.7	(4/15)	N/A ^b	
Aztreonam	N/A ^b		66.7	(12/18)	62.5	(25/40)	61.1	(11/18)
Cefazolin	N/A ^b		100 ^a	(5/5)	94.1	(16/17)	N/A ^b	
Cefuroxime	N/A ^b		100 ^a	(2/2)	83.3 ^a	(5/6)	N/A ^b	
Cefotetan	N/A ^b		0	(0/15)	14.8	(4/27)	N/A ^b	
Ceftriaxone	87.8	(65/74)	94.1	(16/17)	75.6	(31/41)	N/A ^b	
Cefotaxime	97.4	(37/38)	93.8	(15/16)	80.0	(24/30)	N/A ^b	
Ceftizoxime	100	(38/38)	92.9	(13/14)	80.0	(16/20)	100 ^a	(6/6)
Ceftazidime	87.0	(47/54)	66.7	(10/15)	56.7	(17/30)	43.8	(7/16)
Cefepime	87.8	(65/74)	66.7	(12/18)	51.2	(21/41)	43.8	(10/23)
ESBL (+)	—		77.8	(14/18)	64.7	(22/34)	—	
Cefoperazone/sulbactam	49.1	(26/53)	25.0 ^a	(1/4)	45.5	(5/11)	71.4 ^a	(5/7)
Piperacillin/tazobactam	86.2	(50/58)	25.0	(4/16)	16.2	(6/37)	52.9	(9/17)
Tobramycin	73.0	(54/74)	29.4	(5/17)	32.5	(13/40)	30.4	(7/23)
Levofloxacin	63.5	(47/74)	82.4	(14/17)	53.7	(22/41)	39.1	(9/23)
Ciprofloxacin	85.3	(64/75)	77.8	(14/18)	53.7	(22/41)	47.8	(11/23)
Cotrimoxazole	72.2	(52/72)	82.4	(14/17)	65.0	(26/40)	N/A ^b	
Amikacin	52.3	(34/65)	0	(0/18)	12.5	(5/40)	21.7	(5/23)
Gentamicin	81.1	(60/74)	52.9	(9/17)	61.0	(25/41)	30.4	(7/23)
Meropenem	75.0	(18/24)	0 ^a	(0/9)	20.0	(5/25)	28.6 ^a	(2/7)
Ertapenem	N/A ^b		0	(0/16)	16.2	(6/37)	N/A ^b	
Imipenem	86.5	(64/74)	0	(0/17)	14.6	(6/41)	60.9	(14/23)
Polymyxin B	0	(0/40)	0 ^a	(0/3)	0 ^a	(0/9)	25.0 ^a	(1/4)
Tigecycline	7.3	(3/41)	0 ^a	(0/4)	14.3	(2/14)	N/A ^b	
Minocycline	28.6	(10/35)	0 ^a	(0/3)	40.0	(4/10)	N/A ^b	

^a Total case number was less than 10; ^b the bacteria is naturally resistant to this antibiotic.

In this study, 39.3% of recipients developed at least 1 bacterial or fungal infection after LT, which was lower than in 2 Chinese studies in Zhejiang province (68.6% [12] and 51.8% [13]). These differences might be caused by the different definitions of “infection”. In this study, we placed more emphasis on the diagnosis of pathogenic microorganisms. The most common reason for liver transplantation is liver cancer, especially cancer related to hepatitis B. HBV-related liver diseases are still an enormous threat, responsible for 60.7% of all liver transplantation in our study. Most infection (60.0%) occurred in the

first month after LT, which was consistent with other studies. In all the positive culture specimens, *Acinetobacter baumannii* was the most common gram-negative bacteria, which was frequently seen in pneumonia, while *Enterococcus faecium* was the most common gram-positive bacteria, frequently seen in bloodstream infections. Thus, gram-negative bacterial infection was more common than gram-positive bacterial infection [14–16], while fungus infections were the least common and were almost all caused by *Candida spp.*

Table 5. The risk factors of infection for recipients after LT.

Risk factors for infection	Univariate analysis			Multivariate analysis		
	Infection group (n=170)	Non-infection group (n=263)	P	OR	95% CI	P
Age (years), mean±SD	49.32±11.60	46.64±9.36	0.012	1.333 [#]	0.966~1.840 [#]	0.080
Female	24.1 (41/170)	12.9 (34/263)	<0.001	1.174	0.467~2.950	0.733
Albumin (g/L), mean±SD	31.99±4.53	32.02±4.46	0.947			
Blood loss during operation (ml), median (IQR)	1500 (800–3000)	1000 (800–2000)	0.029	1.107 ^{##}	0.989~1.046 ^{##}	0.226
Transfusions during operation						
Transfusions packed RBC (U), median (IQR)	8 (4–12)	5 (2–9)	0.004	1.004	0.986~1.023	0.658
Transfusion FFP (ml), median (IQR)	875 (400–1600)	750 (313–1150)	0.026	1.011 ^{##}	0.941~1.085 ^{##}	0.772
Transfusion autologous RBC,% (n)	42.3 (44/104)	40.3 (58/144)	0.749			
Transfusion Platelet,%(n)	9.6 (10/104)	7.6 (10/145)	0.570			
Transfusion Cryoprecipitate,% (n)	25 (26/104)	17 (25/144)	0.142			
Total transfusion(ml), median (IQR)	2775 (1625–4763)	1900 (775–3588)	<0.001	1.102 ^{##}	0.978~1.048	0.477
Hospital stay (days), median (IQR)	26 (19–43)	21 (16–29)	<0.001	1.034	1.013~1.056	0.002
Postoperative MELD scores, median (IQR)	7 (2–15)	4 (2–7)	<0.001	1.014	0.969~1.062	0.545
Underlying liver disease,% (n)						
Viral cirrhosis	18.8 (32/170)	17.5 (46/263)	0.724			
Alcoholic cirrhosis	3.5 (6/170)	3.8 (10/263)	0.883			
Autoimmune liver disease	2.4 (4/170)	1.5 (4/263)	0.530			
Metabolic disorders	2.4 (4/170)	0.8 (2/263)	0.166			
Liver cancer	36.5 (62/170)	58.9 (155/263)	<0.001	0.644	0.290~1.429	0.279
Liver failure	25.3 (43/170)	9.1 (24/263)	<0.001	2.659	1.019~6.940	0.046
Others	10.6 (18/170)	8.4 (22/263)	0.435			
Mechanical ventilation ≥3 days, % (n)	39.4 (67/170)	9.5 (25/263)	<0.001	3.806	1.567~9.248	0.003
Urinary catheterization ≥3 days, % (n)	83.5 (142/170)	69.6 (183/263)	0.001	1.030	0.385~2.758	0.953
Arteriovenous catheterization ≥3 days, % (n)	62.4 (106/170)	50.2 (132/263)	0.013	1.013	0.501~2.047	0.972

[#] OR value corresponding to per 10 unit change of variable; ^{##} OR value corresponding to per 100 unit change of variable.

The results of antimicrobial susceptibility tests showed that 77.8% of *Escherichia coli* and 64.7% of *Klebsiella pneumoniae* produced extended-spectrum β -lactamases (ESBLs), which were both higher than the whole-hospital level of 53.1–62.5% and 23.3–29.7%, respectively, over the same period, revealing higher resistance rates to penicillins, cephalosporins, and fluoroquinolones. For *Escherichia coli*, the most sensitive antibiotics were carbapenems, amikacin, cefotetan, and nitrofurantoin. For *Klebsiella pneumoniae*, the most sensitive antibiotics

were polymyxin B, followed by amikacin, cefotetan, carbapenems, piperacillin/tazobactam, and tigecycline. For *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, the alternative antibiotics seemed relatively limited – *Pseudomonas aeruginosa* restricted to amikacin, and *Acinetobacter baumannii* restricted to polymyxin B and tigecycline. These results will help us to perform effective empirical antibiotic treatment before the pathogenic evidence is available.

Table 6. The risk factors for death with infection after LT.

Risk factors for death with infection	Univariate analysis			Multivariate analysis		
	Death (n=26)	Survival (n=144)	P	OR	95% CI	P
Age (years), mean±SD	50.23±10.08	49.15±11.87	0.664			
Female	46.2 (12/26)	20.1 (29/144)	0.004	3.755	0.555~25.384	0.175
Albumin (g/L), mean±SD	32.80±4.56	31.85±4.53	0.336			
Blood loss during operation (ml), median (IQR)	2000 (1350–3750)	1500 (800–2500)	0.016	1.008##	0.935~1.088##	0.832
Transfusions during operation						
Transfusions packed RBC (IU), median (IQR)	11 (7–16)	7 (4–10)	0.015	1.081	0.837~1.396	0.549
Transfusion FFP (ml), median (IQR)	1375 (713–1600)	800 (400–1600)	0.159			
Transfusion autologous RBC, % (n)	50.0 (8/16)	40.9 (36/88)	0.498			
Transfusion platelet, % (n)	0 (0/16)	11.4 (10/88)	0.156*			
Transfusion Cryoprecipitate, % (n)	18.8 (3/16)	26.1 (23/88)	0.530			
Total transfusion (ml), median (IQR)	4150 (2875–6075)	2575 (1475–4500)	0.040	1.012##	0.913~1.123##	0.816
Postoperative MELD score, median (IQR)	19 (10–26)	6 (1–12)	<0.001	1.120	1.020~1.230	0.017
Underlying liver disease,% (n)						
Viral cirrhosis	23.1 (6/26)	18.1 (26/144)	0.547			
Alcoholic cirrhosis	3.8 (1/26)	3.5 (5/144)	0.924			
Autoimmune liver disease	3.8 (1/26)	2.1 (3/144)	0.585			
Metabolic disorders	0 (0/26)	2.8 (4/144)	0.390*			
Liver cancer	34.6 (9/26)	36.8 (53/144)	0.831			
Liver failure	19.2 (5/26)	26.4 (38/144)	0.440			
Others	15.4 (4/26)	9.7 (14/144)	0.388			
Septic shock, % (n)	61.5 (16/26)	5.6 (8/144)	<0.001	12.000	1.124~128.066	0.040
Multi-site infection, % (n)	58.3 (14/24)	33.9 (39/115)	0.025	2.582	0.240~27.778	0.434
Multi-pathogen infection, % (n)	50.0 (12/24)	53.0 (61/115)	0.786			
Mechanical ventilation ≥3 days, % (n)	75.4 (17/26)	34.7 (50/144)	0.003	1.201	0.188~7.684	0.846
Urinary catheterization ≥3 days, % (n)	96.2 (25/26)	81.2 (117/144)	0.059			
Arteriovenous catheterization ≥3 days, % (n)	65.4 (17/26)	61.8 (89/144)	0.729			

* Fisher's exact test; # OR value corresponding to per 10 unit change of variable; ## OR value corresponding to per 100 unit change of variable.

Age, sex, MELD scores, severe hepatitis, mechanical ventilation, post-transplant hospital time, renal failure, portal vein thrombosis, and biliary complications were significantly associated with bacterial and fungal infection in multiple studies [8,12,13,17–21]. To investigate the possible risk factors for bacterial and fungal infections after LT, we compared the

infection group (n=170) and non-infection group (n=263), and found that prolonged hospital stay, liver failure, and mechanical ventilation were independent risk factors for infection after LT. It seemed that hospital stay was a risk factor for infection after LT, but we should realize there is a reciprocal relationship between hospital stay and infection. One the one hand,

Table 7. Clinical data of 16 septic shock patients in the death with infection group.

Number	Age (years)	Sex	Underlying liver disease	MELD score	Pathogens	Antimicrobial agents and duration(days)
1	54	Female	Hepatitis B, cirrhosis	16	<i>Staphylococcus epidermidis</i> (BSI), CRAB (Pneumonia)	Cefoperazone/sulbactam (7); Imipenem (5); Ciprofloxacin (7); Voriconazole (6); Vancomycin (1)
2	45	Female	Autoimmune hepatitis	23	<i>Enterococcus faecium</i> (UTI), CRAB (Pneumonia)	Cefoperazone/sulbactam (13); Tigecycline (3)
3	45	Female	Polycystic liver	40	–	Imipenem (1)
4	45	Female	Cholestatic cirrhosis	6	CRAB (BSI)	Piperacillin/tazobactam (7); Cefoperazone/sulbactam (2); Imipenem (2); Voriconazole (4); Vancomycin (2)
5	27	Male	HCC, hepatitis B-related	37	<i>Enterococcus faecium</i> (UTI), CRAB and <i>Hafnia alvei</i> (Pneumonia)	Cefoperazone/sulbactam (8); Piperacillin/tazobactam (1); Imipenem (1)
6	61	Female	Hepatitis B, cirrhosis	10	<i>Enterococcus faecium</i> (UTI)	Cefoperazone/sulbactam (5); Vancomycin (1)
7	62	Male	Hepatitis B, cirrhosis	21	CRAB, <i>Stenotrophomonas maltophilia</i> and <i>Pseudomonas aeruginosa</i> (Pneumonia), <i>Candida parapsilosis</i> (BSI)	Cefoperazone/sulbactam (16); Imipenem (13); Levofloxacin (5); Voriconazole (9)
8	50	Male	Hepatitis B, cirrhosis	10	CRAB (BSI and Pneumonia), <i>Pseudomonas aeruginosa</i> and <i>Candida albicans</i> (Pneumonia), <i>Escherichia coli</i> (SBP)	Cefoperazone/sulbactam (22); Ciprofloxacin (7); Vancomycin (2); Imipenem (9); Voriconazole (4); Piperacillin/tazobactam (1)
9	46	Male	Alcoholic cirrhosis	25	CRAB (BSI)	Cefoperazone/sulbactam (8); Imipenem (3)
10	47	Male	HCC, hepatitis B-related	7	–	Cefoperazone/sulbactam (12); Imipenem (6); Vancomycin (1); Piperacillin/tazobactam (1)
11	58	Female	Hepatitis C, cirrhosis	19	CRAB (SBP and Pneumonia)	Cefoperazone/sulbactam (10); Imipenem (1)
12	65	Male	HCC, hepatitis B-related	6	CRAB (BSI and Pneumonia)	Piperacillin/tazobactam (10); Imipenem (1); Vancomycin (1); Cefoperazone/sulbactam (2)
13	56	Male	Alcoholic cirrhosis	22	CRAB (BSI and Pneumonia)	
14	37	Male	HCC, hepatitis B-related	26	CRAB (Pneumonia)	Micafungin (2)
15	56	Male	Liver failure, hepatitis B-related	19	CRAB and <i>Aspergillus</i> (Pneumonia), <i>Enterococcus faecium</i> (BSI and SBP)	Cefminox (1); Meropenem (3); Caspofungin (1); Cefoperazone/sulbactam (1); Linezolid (1)
16	41	Male	HCC	36	CRAB (Pneumonia), <i>Enterococcus faecium</i> (BSI)	Cefoperazone/sulbactam (9); Imipenem (6); Micafungin (5);

CRAB – carbapenem resistant *Acinetobacter baumannii*; HCC – hepatocellular carcinoma; UTI – urinary tract infection; BSI – blood stream infection; SBP – spontaneous bacterial peritonitis.

prolonged hospitalization may increase the risk for nosocomial infections; on the other hand, the infection can also prolong the time of hospitalization. Preoperative diagnosis of liver failure, but not postoperative MELD scores, was an independent predictor of infection after LT, suggesting that for patients with liver failure, more attention should be paid to the use of antibiotics before surgery and the monitoring of symptoms and indicators of postoperative infection. In particular, as long as the patient can tolerate it, early removal of mechanical ventilation will reduce the possibility of infection for LT patients.

Postoperative MELD scores were a predictor for infected-related death. Research has shown that the preoperative MELD score cannot predict recipient survival [22]. Our research showed that high postoperative MELD scores indicated a higher risk of death for infected patients, so it is necessary for clinicians to immediately evaluate MELD scores after LT in order to better care and treat patients. Moreover, the severe acute infection-septic shock was an independent predictor, as in multiple studies [5,23,24]. Kyo Won Lee [25] reported that the implantation of ECMO (extracorporeal membrane oxygenation) might be considered in highly selected LT recipients with refractory septic shock. Since septic shock was closely related to the death of LT patients, early diagnosis of septic shock will benefit patients' survival. Researchers believed that the Sepsis-3 standard was based on the latest understanding of the pathobiology, treatment, and epidemiology of sepsis, which was accepted as a more specific and sensitive definition compared with the previous definitions of sepsis [26]. Furthermore, in the 16 patients of septic shock, up to 13 cases (81.25%) isolated Carbapenem-resistant *Acinetobacter baumannii* (CRAB). CRAB infection recipients had a mortality rate of 46.4% within 60 days after surgery, and preoperative CRAB acquisition was a risk factor for CRAB infection after LT [27]. Therefore, patients with the above-mentioned infection risk factors can be routinely screened for CRAB before

operation so that once infection occurs, they can use targeted antibiotics, even before getting the evidence of etiology. From the perspective of antibiotic use, the most commonly used antibiotics in patients with septic shock were Cefoperazone/sulbactam and Imipenem, which didn't cover CRAB, and only one patient used tigecycline which may be effective for CRAB. Current treatments for CRAB are very limited. Antibiotics that may be effective include polymyxins, tigecycline, fosfomycin, and ceftazidime/avibactam, and often require a combination. For patients with preoperative screening for CRAB colonization, once septic shock occurs, care should be taken with CRAB infection and the possibility of using effective antibiotics such as tigecycline should be considered.

Conclusions

We found that 39.3% of recipients had at least 1 bacterial or fungal infection after LT. *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* were the most common gram-negative bacteria and *Enterococcus faecium* was the most common gram-positive bacteria in LT postoperative infection. Shortening the length of hospital stay and early withdrawal of mechanical ventilation reduce the risk of infection after LT. Patients with liver failure should be more vigilant against postoperative infection. Once an infection occurs, immediate assessment of the postoperative MELD score, early diagnosis of septic shock, and active search for pathogenic evidence for precise treatment will help improve patient prognosis. Since CRAB infection is the main pathogenic bacteria causing septic shock in transplant patients, CRAB colonization should be routinely screened for before surgery for patients with the above-mentioned risk factors so that once infection occurs, antibiotics can be empirically used before the culture results are available.

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