Infection within 2 weeks before liver transplantation closely related to prognosis of posttransplant infection: a single-center retrospective observational study in China

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Abstract

Background Infections still represent the main factors influencing morbidity and mortality following liver transplantation. This study is to evaluate the incidence and risk factors for infection and survival after liver transplantation. **Methods** We retrospectively examined medical records in 210 recipients who underwent liver transplantation between April 2015 and October 2017 in our center. **Results** During the median follow-up days of 214, the incidence of infection after liver transplantation was 46.7% (n=98): namely, pneumonia (43.4%), biliary tract infection (21.9%) and peritonitis (21.4%). Among the pathogens in pneumonia, the most frequently isolated was *Acinetobacter baumannii* (23.5%) and *Klebsiella pneumoniae* (21.1%). For biliary tract infection, the first rank was *Streptococcus maltophilia* (14.0%) and then *Klebsiella pneumoniae* (11.6%). *Pseudomonas aeruginosa*, *Streptococcus maltophilia*, and *Klebsiella pneumoniae* accounted for 21.4%, 11.9% and 11.9% of pathogens in peritonitis, respectively. The independent risk factors for infection after liver transplantation are model for end-stage liver disease (MELD) or pediatric end-stage liver disease (PELD) score, total blood loss in operation and duration of drainage tube. All-cause mortality was 11.0% (n=23). The prognostic factors for postoperative infection in transplant recipients are infection, especially pneumonia within 2 weeks before transplantation, complication with impaired renal function and higher MELD or PELD score after 7 days of transplantation. Kaplan–Meier curves of survival showed that recipients with infection within 2 weeks before transplantation had a significantly lower cumulative survival rate compared with those without infection (66.7% vs 91.9%, HR=4.480, 95% CI, 3.377-47.85; $p<0.001$). **Conclusions** Infection, especially pneumonia within 2 weeks before transplantation are independent prognostic factors for postoperative infection in transplant recipients.

Background

Liver transplantation remains an effective procedure for multiple end-stage liver diseases. With the widespread use of potent immunosuppressive agents, the incidence of allograft rejection was reduced while opportunistic infections increased. Despite efficacious antimicrobial prophylaxis and vaccination to some pathogens, infections still represent the main factors influencing morbidity and mortality following liver transplantation.¹⁻⁵

In infections after liver transplantation, epidemiologic exposures included donor-derived infections and recipient-derived infections. Transplanted organs facilitate the transmission of infections from organ donors.¹ Colonized or latent infections of recipients could be activated due to immunosuppression state after transplantation. However, the data about these were rare.

According to several previous reports, the spectrum of major infections occurring after transplantation has undergone a striking evolution⁴. So, knowledge of pathogen spectrum was very useful to help effective empirical treatment. In this study, we surveyed infection rate and pathogen distribution after liver transplantation and analyzed the impact of donor or recipient factors on infection and survival.

Methods

General population

This was a retrospective, single center research. A total of 217 consecutive patients who underwent liver transplantation between April 2015 and October 2017 were eligible to participate in the research. 7 patients were excluded because they died within 7 days after transplantation. At last, 210 patients were included in the study. Patient records were reviewed at the end of the study and follow-up information was obtained from referring physicians. Surveillance viral load testing for cytomegalovirus (CMV) were performed every week for the first month after transplant. Other cultures were ordered as dictated by the clinical situation. The study was approved by the hospital's ethics committee.

Surgery and immunosuppression

All patients underwent orthotopic liver transplantation either with primary anastomosis of the bile duct or choledochojejunostomy.

Standard immunosuppression often included tacrolimus (FK506), mycophenolate (MMF) and corticosteroids. FK506 was initially administered at a dosage of 3mg every 12 hours orally as soon as the patient was able to take oral medication, usually less than three days after surgery. FK506 was then adjusted according to blood levels. The target level for tacrolimus was 10–12 ng/ml during the first month and 8–10 ng/ml after the second month. Oral MMF was given at the dosage of 500mg twice a day after 12 days of surgery. 240mg of methylprednisolone was administered intravenously on the day of surgery. This was reduced to 180 mg on the day after surgery and then rapidly tapered so that by day 6 the patient was receiving 40 mg of methylprednisolone. Oral therapy with an equivalent dose of prednisone was employed when the patient was able to take oral medicine. Baxilimab (20mg) was given intravenously in the surgery as dictated by clinical situation.

Antimicrobial treatment

Once recipients were diagnosed as infection, they would receive empirical antimicrobial treatment, then turning to etiological treatment after the results of culture and susceptibility were applicable. When viral load testing for CMV was positive, intravenous ganciclovir 250mg every 12 hours was given until viral eradication was achieved, but not shorter than 2 weeks.

Definition of infections

We attempted to identify all infections which occurred after transplantation and categorize them according to time after transplantation, site of infection, type of pathogen, and outcome. Strict criteria were employed to define infections included in this study. They are as follows:

Bloodstream infection was defined by the isolation in at least 1 blood culture of *Listeria monocytogenes*, *Staphylococcus aureus*, *Candida* species or aerobic gram-negative rods. For other pathogens, the isolation of the bacteria in 2 blood cultures or in 1 positive blood culture and in a culture from a known site of infection was required.

Abdominal infection was diagnosed if the peritoneal neutrophil count was > 200 polymorphonuclear cells and if a pathogen was isolated. In cases where no cell counts were obtained, a Gram stain of peritoneal fluid showing ≥ 1 polymorphonuclear cell per oil field was sufficient.

Biliary tract infection required the presence of fever, right upper quadrant pain, and elevation of liver function tests together with either evidence of cholangitis on liver biopsy or isolation of the same organism from both the T-tube drain and blood.

Pneumonia required the appearance of new infiltrates on chest radiograph, the onset of new respiratory symptoms (cough, dyspnea) or hypoxemia, and the isolation of bacteria in heavy growth from purulent sputum. A diagnosis of CMV pneumonia also required a temperature elevation $\geq 38^{\circ}\text{C}$ for at least 2 days within a 4-day period, the presence of neutropenia or thrombocytopenia, and the detection of CMV DNA in blood.

Statistical analysis

Univariate and multivariate analysis were used to find the risk factors and prognostic factors for infection after transplantation. We used Mann-Whitney U test and chi-square test for the univariate analysis and all variables with a p value < 0.05 were defined as significant. We further conducted logistic regression for the multivariate analysis with factors proved to be significant. The Kaplan–Meier method was used to calculate the overall survival in the recipients who got infection after transplantation. All analyses were performed using Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL) and Graphpad Prism, version 6.02 (Graphpad Software, San Diego, CA, USA).

Results

Spectrum of patient information and incidence of postoperative infection

Of all the 210 patients in this study, the most common underlying disease was viral hepatitis (139 cases, 66.2%), then inherited liver diseases (24 cases, 11.4%) and autoimmune liver disease (16 cases, 6%) (Table 1). In total, 196 episodes of infection occurred after transplantation during the median following days of 214. Every patient experienced on average 0.93 episodes of infection. In all, 98 patients were defined as postoperative infection, and the incidence of infection reached 46.7%. (Figure 1)

The most frequent pathogen was *Enterobacteriaceae* with 41 episodes, including *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Serratia marcescens*. The second most common isolated organism was *Acinetobacter baumannii* (27 cases), which only occurred in 1 month after transplantation. *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* was isolated in 21 and 22 cases, respectively. Regarding viral infection, cytomegalovirus was the most common with 12 episodes.

In total, 12 episodes of fungal infection were noted, and the most frequent pathogen was *Candida albicans* (10 cases). (Table 2)

Sites of infection and microbial aetiology

Respiratory tract was the most common site of infection (43.4%), then biliary tract (21.9%), abdomen (21.4%) and bloodstream (7.6%). Among the pathogen in pneumonia, the most frequently isolated was *Acinetobacter baumannii* (23.5%) and *Klebsiella pneumoniae* (21.1%). *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Klebsiella pneumoniae* accounted for 21.4%, 11.9% and 11.9% of pathogens in peritonitis, respectively. For biliary tract infection, the first rank was *Stenotrophomonas maltophilia* (14%), then *Klebsiella pneumoniae* (11.6%), while *Pseudomonas aeruginosa* and *Enterococcus faecium* (9.3%) were in the equal third place. Only 15 episodes of bloodstream infection occurred, and *Staphylococcus* was the most common pathogen. (40%, Figure 2)

Risk factors for infection after liver transplantation

In univariate analysis, we found infection-related factors included: age, model for end-stage liver disease (MELD) or pediatric end-stage liver disease (PELD) score and infection within 2 weeks before transplantation, especially pneumonia other than peritonitis, amount of blood loss and duration time of drainage tube (Table 3). In multivariate analysis, the independent risk factors of infection after liver transplantation are MELD or PELD before transplantation (18.2 vs 12.4, $p=0.002$), amount of blood loss in operation (2.3L vs 1.1L, $p=0.002$) and duration time of drainage tube (29.6d vs 12.8d, $p=0.009$).

Recipient survival and prognostic factors for infection after liver transplantation

During the median follow-up days of 214, all-cause mortality was 11.0% (23/210). The causes of death included three main categories: infection, poor graft function and others. 42% was infection-associated death, while poor graft function accounted for 29%. In a total of 98 patients with infection after transplantation, 82 people survived. (Figure 1) In the univariate analysis, infection within 2 weeks before transplantation (especially pneumonia other than peritonitis), estimated glomerular filtration rate (eGFR) <50ml/min after transplantation and MELD or PELD score before or after 7 days of transplantation

were identified as prognostic factors (Table 4). Multivariate analysis revealed that independent prognostic factors were infection within 2 weeks before transplantation (OR 5.3, 95%CI, 1.143-24.578) and MELD or PELD score after 7 days of transplantation (OR 1.298, 95%CI, 1.105-1.526, Table 3). When recipients suffered from infection within 2 weeks before transplantation, although infection was controlled on the day of transplantation, they had a significantly lower survival compared to those not infected in Kaplan-Meier analysis (67.6% vs 91.3%, HR=4.480, 95%CI, 3.377-47.85; $p<0.001$, Figure 3).

Discussion

Among all the liver transplant recipients, infection is a problem to be concerned. Comparing to patients with normal immune function, the diagnosis of infection is delayed because diminished signs and symptoms. Also, the spectrum of potential pathogens is broader and infection often progress more rapidly¹.

So, it is very important to learn the risk and prognostic factors of infection after liver transplantation. In our study, MELD or PELD score is the major risk and prognostic factor regarding to infection after transplantation, which is similar to other studies.⁶⁻⁸ MELD or PELD score are used to evaluate the liver function of patients waiting to process liver transplantation, either in adult or pediatric.⁹⁻¹⁰ With extreme poor hepatic function, these recipients might have a lower level of immune defense against invasive microbial. We also found whether MELD or PELD score recover to normal after transplantation is associated with survival rate, like other studies reported¹¹⁻¹². With failed recovery of liver function after liver transplantation, patients suffering from infections are more likely to be not survived.

In our hospital, the incidence of infection after liver transplantation reached 46.7%. It was consistent with the previous reports studied in China, in which 15%-69% of patients acquired postoperative infection¹³⁻¹⁷. Most infection occurred in the first month after liver transplantation, which is related to surgical complications as for traditional view¹⁸. However, the most common site of infection is not surgical site, but the respiratory tract and Gram-negative pathogens are major pathogens. Our findings were also supported by other studies in China¹⁴⁻¹⁵. These indicated that the pattern of posttransplant infection was changed and nosocomial infection might be the most important epidemiological exposure in the first month after transplantation in China.

The reason for most Chinese patients receiving liver transplantation is cirrhosis based on chronic hepatitis B¹⁹. As we found in the study, viral hepatitis accounts for 65.3% of underlying disease. Spontaneous bacterial peritonitis is a common complication of cirrhosis. Meanwhile, pneumonia and biliary tract infection are also not rare in the case of chronic cirrhosis. As a result, a large number of patients got infection before transplantation.

It is recommended that active infection in transplant recipients should be controlled before transplantation, since immunosuppression will exacerbate the infectious process.¹ In this study, there were 18 patients (8.6%) having infections within 2 weeks before transplantation. Although their infections were all controlled on the day of transplantation, it remained to be a risk and prognostic factor for infection after transplantation. Among all the infections, pneumonia seemed to be more related than other infections. In 20 patients suffering pneumonia within 2 weeks before transplantation, 15 patients (75%) got pneumonia again after transplantation. While among 244 patients without pneumonia before, only 98 (40.2%) got pneumonia after transplantation. ($p=0.004$, data not shown). We assume the explanation might be that the pathogens become latent, aren't eradicated or enough due to lack of treatment course and cause poorer liver function, especially for the respiratory tract, ≤ ad ∈ t prove these infections are exactly recipient-derived, infections within 2 weeks before transplantation should be paid close attention.

This study had some limitations. First, this is a single center study, and the results can be biased because of different pathogen distribution and higher antibiotic resistance rate than other medical institutions in China. Second, our study was retrospective, and the lack of some information, such as bile complication information other than infection, might cause some biases in data statistics.

Conclusions

We concluded that risk factors for infection after liver transplantation are MELD or PELD score and infection, especially pneumonia within 2 weeks before transplantation. The prognostic factors for postoperative infection in transplant recipients are infection, especially pneumonia within 2 weeks before transplantation, complication with impaired renal function and MELD or PELD score after 7 days of transplantation.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Huashan hospital, Fudan University. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Author`s contributions

Y.Y participated in the performance of the research, in the writing of the paper, and in data analysis. R.D.L participated in the performance of the research and in the admission and management of the patients. J.W.A participated in data analysis. Y.M.Z, X.Z, Y.Y.Q, X.C.C, X.Y.W, H.C.Z, Y.L and S.S.W participated in the data collection. T.G. participated in general supervision of infection control service and in the performance of the research. Y.Q.Y participated in research design and data analysis. Y.F.T and X.F.Z. participated as general supervision of transplant unit and in the performance of the research. W.H.Z. participated in the revising the article. Y.X.H. and Z.X.W. participated in research design, in the performance of the research and in the writing of the article.

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Tables

Table 1 Recipient characteristics

Liver transplantation recipients (n=210)	
Age, mean (range)	45.1 (0.6-69)
Gender (Male), n (%)	167 (79.5)
Underlying disease	
Viral hepatitis, n (%)	139 (66.2)
Inherited disease, n (%)	24 (11.4)
Autoimmune liver disease, n (%)	11 (5.2)
HCC, n (%)	11 (5.2)
Toxic (alcohol or drug-related), n (%)	13 (6.2)
Cirrhosis, unknown etiology, n (%)	3 (1.4)
Others, n (%)	9 (4.3)

HCC, hepatocellular carcinoma

Table 2 Common pathogens of different periods after liver transplantation

Pathogen	<1 Month	1-3 Months	>3 Months	Total
<i>Enterobacteriaceae</i>	28	10	3	41
<i>Acinetobacter baumannii</i>	27	0	0	27
<i>Pseudomonas aeruginosa</i>	19	2	0	21
<i>Stenotrophomonas maltophilia</i>	18	1	3	22
<i>Staphylococcus</i>	14	1	3	18
<i>Enterococcus</i>	10	2	2	14
<i>Cytomegalovirus</i>	9	3	0	12
<i>Fungus</i>	10	1	1	12

Table 3 Risk factors of infection after liver transplantation

Variables	With infection (n=98)	Without infection (n=112)	P value	P value-MA
Preoperative variables				
Age, mean (range)	48.1 (3-69)	42.4 (0.6-67)	0.016	
Gender (Male), n (%)	78 (79.6)	89 (79.5)	1.000	
Diabetes, n (%)	22 (22.4)	18 (16.1)	0.291	
MELD or PELD before LT, mean (range)	18.2 (3-43)	12.4 (-9-46)	<0.001	0.002
Infection within 2 weeks before LT, n (%)	18 (18.4)	6 (5.4)	0.004	
Pneumonia before LT	11 (11.2)	3 (2.7)	0.023	
Peritonitis before LT	5 (5.1)	2 (1.8)	0.255	
Intraoperative variables				
Duration of operation, mean (range), hours	7.95 (5-20.5)	7.74 (4.5-19)	0.494	
Blood loss, mean (range), L	2.3 (0.2-22)	1.1 (0.1-5)	<0.001	0.002
Biliary anastomosis: Roux-en-Y, n (%)	4 (4.1)	11 (9.8)	0.178	
Postoperative variables				
Immunosuppression with baxilimab, n (%)	12 (12.2)	15 (13.4)	0.839	
Reoperation, n (%)	10 (10.2)	4 (3.6)	0.093	
Rejection, n (%)	12 (12.2)	8 (7.1)	0.243	
Duration time of drainage tube, day	29.6 (3-282)	12.8 (1-66)	<0.001	0.009

LT, liver transplantation; MELD, model for end-stage liver disease; PELD, pediatric end-stage liver disease; DCD, donation after cardiac death

Table 4 Univariate risk factors of mortality in 98 patients with postoperative infection

Variable	Survival (n=82)	Death (n=16)	P value	P value-MA	Odds ratio	95% confidence interval
Age, mean (range)	47.83 (3-67)	49.56 (5-69)	0.663			
Gender (Male), n (%)	68 (82.9)	10 (62.5)	0.088			
Infection within 2 weeks before LT, n (%)	11 (13.4)	7 (43.8)	0.009	0.033	5.300	1.143-24.578
Pneumonia before LT	6 (7.3)	5 (31.2)	0.016			
Peritonitis before LT	2 (2.4)	3 (18.8)	0.030			
MELD or PELD before LT, mean (range)	17.7 (3-43)	20.8 (6-37)	0.248			
MELD or PELD after 7 days of LT, mean (range)	14.0 (8-28)	23.7 (15-43)	0.003	0.002	1.298	1.105-1.526
Rejection, n (%)	12 (14.6)	0 (0)	0.206			
Complication after LT						
eGFR<50ml/min after LT, n (%)	10 (12.2)	8 (50.0)	0.002			
Hepatic encephalopathy, n (%)	4 (4.9)	0 (0)	1.000			

LT, liver transplantation; MA: Multivariate analysis; MELD, model for end-stage liver disease; PELD, pediatric end-stage liver disease

Figures

Figure 1

Flow chart of infections and survival after liver transplantation. LT, liver transplantation.

■ *Acinetobacter baumannii* ■ *Klebsiella pneumoniae* ■ *Streptophomonas maltophilia*
 ■ *Staphylococcus* ■ *Pseudomonas aeruginosa* ■ *Enterococcus faecium*
 ■ Cytomegalovirus ■ Fungus ■ Others

Figure 2
Frequency of different pathogens and sites of infections after liver transplantation.

Figure 3
Among transplant recipients with postoperative infection, survival rates of patients with and without infection within 2 weeks before transplantation. Although infection was controlled on the day of transplantation, recipients who got infection within 2 weeks before transplantation had a significantly lower survival compared to those not infected (66.7% vs 91.9%, HR=4.480, 95%CI, 3.377-47.85; $p<0.001$). The dotted lines indicated 95% confidence interval. LT, liver transplantation.