World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i16.1975

World J Gastroenterol 2012 April 28; 18(16): 1975-1980
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Analysis of infections in the first 3-month after living donor liver transplantation

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Supported by The National Science and Technology Major Project of China, No. 2012ZX10002-016 and 2012ZX10002017-006
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Received: August 29, 2011 Revised: December 2, 2011
Accepted: March 10, 2012
Published online: April 28, 2012

Abstract

AIM: To identify factors related to serious postoperative bacterial and fungal infections in the first 3 mo after living donor liver transplantation (LDLT).

METHODS: In the present study, the data of 207 patients from 2004 to 2011 were reviewed. The pre-, intra- and post-operative factors were statistically analyzed. All transplantations were approved by the ethics committee of West China Hospital, Sichuan University. Patients with definitely preoperative infections and infections within 48 h after transplantation were excluded from current study. All potential risk factors were analyzed using univariate analyses. Factors significant at a $P < 0.10$ in the univariate analyses were involved in the multivariate analyses. The diagnostic accuracy of the identified risk factors was evaluated using receiver operating curve.

RESULTS: The serious bacterial and fungal infection rates were 14.01% and 4.35% respectively. *Enterococcus faecium* was the predominant bacterial pathogen, whereas *Candida albicans* was the most common fungal pathogen. Lung was the most common infection site for both bacterial and fungal infections. Recipient age older than 45 years, preoperative hyponatremia, intensive care unit stay longer than 9 d, postoperative bile leak and severe hyperglycemia were independent risk factors for postoperative bacterial infection. Massive red blood cells transfusion and postoperative bacterial infection may be related to postoperative fungal infection.

CONCLUSION: Predictive risk factors for bacterial and fungal infections were indentified in current study. Pre-, intra- and post-operative factors can cause postoperative bacterial and fungal infections after LDLT.

Key words: Bacterial infection; Fungal infection; Living donor liver transplantation

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Li C, Wen TF, Mi K, Wang C, Yan LN, Li B. Analysis of infections in the first 3-month after living donor liver transplantation. *World J Gastroenterol* 2012; 18(16): 1975-1980 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i16/1975.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i16.1975

INTRODUCTION

Despite the major advances in immunosuppressant regimens, perioperative management and medical care have contributed to improvements in the survival rate of solid organ transplant recipient, infection continues to be a leading cause of postoperative mortality and morbidity resulting from the poor preoperative condition, immunosuppressive therapy and exposure to nosocomial pathogens[1,2]. Liver transplantation has one of the highest rates

of postoperative infection among all sold organ transplant procedures[3]. It has been reported that the postoperative bacterial infection rate may up to more than 60% and accounted for an in-hospital mortality rate of 30%-50%[4]. Previous studies have reported that the incidence of postoperative fungal infection ranged from 5% to 40%, and the mortality associated with fungal infection was between 25% and 69%[5]. Moreover, the mortality of patient with *aspergillus* has been found to approach 100% if untreated[6]. Accordingly, to identify which factors may cause postoperative bacterial and fungal infections is important to transplant surgeon. However, this issue is still not well established until now. In current study, we used a large cohort to identify the pattern and risk factors associated with postoperative bacterial and fungal infections that occurred within the first 3 postoperative months after living donor liver transplantation.

MATERIALS AND METHODS

Study group

Patients who received adult-to-adult living donor liver transplantation (LDLT) from 2004 to 2011 at our center were considered in present study. All transplantations were approved by the ethics committee of West China Hospital, Sichuan University. Patients with definitely preoperative infections and infections within 48 h after transplantation were excluded from current study.

Donor selection

Donors must be healthy close relatives with compatible ABO blood types. Serological testing for viral hepatitis and human immunodeficiency virus antibodies as well as testing for other acute or chronic diseases was negative. Volumetric computed tomography with contrast was performed to evaluate the hepatic volume of the donors. Right hepatic lobe without middle hepatic vein of the donors need to be at least 0.8% of the recipient's standard weight and the remnants must be at least 40% of the donor's liver volume. Magnetic resonance cholangiopancreatography was performed to assess the anatomy of the biliary tree[7,8].

Immunosuppression

The postoperative immunosuppression consisted of tacrolimus, mycophenolate mofetil and steroids. Steroids were withdrawn as soon as possible. Acute rejection episodes were confirmed by pathology. Steroid pulse therapy was conducted to patient with rejection[9]. OKT3 monoclonal antibody was administrated to patients with persistent rejection or steroid-resistant rejection. When necessary, these treatments were repeated[10].

Infection prophylaxis

Antimicrobial prophylaxis consisted of Cefoperazone and Sulbactam for three to five days. Fluconazole was administrated to patients with risk factors of fungal infection for one to two weeks after liver transplantation.

Definitions

Serious infection was defined as the culture-positive bacterial or fungal infection in blood, sputum, urine, or ascetic fluid which was obtained on the basis of clinical suspicion of an infection[11,12]. Preoperative renal dysfunction was defined as the level of serum creatinine greater than 1.5 mg/dL[13]. Bile leak was defined as bilirubin concentration in the drainage greater than the plasma level[14]. Model for end-stage liver disease (MELD) scores were calculated according to the formula: MELD score = 9.57 × Ln creatinine (mg/dL) + 11.2 × (Ln INR) + 3.78 × Ln bilirubin (mg/dL) + 6.43[15]. Massive red blood cells (RBCs) transfusion was defined as transfusion not less than 6 packed RBCs in the first 24 h of surgery[16]. Severe hyperglycemia was defined as glucose concentrations more than or equal to 20 mg/dL[17]. Hyponatremia was defined as a serum sodium concentration of less than 130 mEq/L[18].

Statistical analysis

All continuous variables were presented as mean ± SD and compared using one way analysis of variance. χ^2 test or Fisher's exact test was used for comparing categorical variables. Independent risk factors were identified by Cox regression. Factors significant at a $P < 0.10$ in the univariate analyses were involved in the multivariate analyses. The diagnostic accuracy of the identified risk factors was evaluated using receiver operating curve (ROC). All analyses were performed using SPSS 16.0. We considered a P value of less than 0.05 to be significant.

RESULTS

Patient characteristics

A total of 207 patients were included in current study. The mean age was 42.93 ± 8.77 years for the recipients, whereas the mean age was 34.83 ± 9.99 years for the donors. Twenty-seven patients were female, whereas eighty-one donors were female. Nine patients had pretransplant diabetes mellitus. Sixteen patients suffered from preoperative renal dysfunction. The mean MELD score was 16.40 ± 9.84. The mean graft to recipient weight ratio (GRWR) was 0.94% ± 0.18%. The causes for transplantation were hepatitis B (n = 116), hepatocellular carcinoma (n = 75), hepatolithiasis (n = 3), hepatitis C (n = 3), alcoholic cirrhosis (n = 3), polycystic liver (n = 1), primary biliary cirrhosis (n = 2), hepatic hydatidosis (n = 1), huge hepatic hemangioma (n = 1), trauma (n = 1), autoimmune hepatitis (n = 1).

Pattern of infection

During the first 3 postoperative months, serious bacterial infection was observed in 29 recipients, whereas serious fungal infection was found in 9 patients. Among the 9 patients with fungal infection, 6 patients were combined with or secondary to bacterial infection. Only 3 patients infected fungal infection alone. Four patients had two kinds of bacterial infection. One patient suffered from three kinds of bacterial infection. *Enterococcus faecium* (n = 8) was the most common pathogen in patients with bacterial infec-

Table 1 Univariate analysis for risk factors for postoperative bacterial infection

Variables	Infected	No infected	*P* value
Donor variables			
Age (yr)	34.45 ± 8.78	34.89 ± 10.19	0.825
Gender (female)	10	71	0.580
BMI (kg/m^2)	22.80 ± 2.69	22.99 ± 2.53	0.711
Recipient variables			
Age (yr)	46.72 ± 8.27	42.31 ± 8.63	0.012
Gender (female)	2	25	0.384
BMI (kg/m^2)	21.77 ± 4.21	22.63 ± 2.93	0.172
MELD score	17.24 ± 7.40	16.26 ± 10.18	0.621
Renal dysfunction	1	15	0.705
Diabetes mellitus	1	8	0.798
Starting albumin level < 2.8 g/dL	10	32	0.040
Starting TB level ≥ 20 mg/dL	3	24	0.774
Starting INR level	1.62 ± 0.54	1.71 ± 1.50	0.744
Hyponatremia	7	12	0.008
Graft variables			
GRWR (%)	0.99 ± 0.23	0.93 ± 0.17	0.111
Intraoperative variables			
Massive RBCs transfusion	8	35	0.335
FFP transfusion > 10 units	7	42	0.949
Postoperative variables			
Bile leak	10	6	0.000
Rejection	2	3	0.090
Hyperglycemia	5	10	0.042
ICU stay	17.38 ± 11.11	12.28 ± 12.48	0.040

BMI: Body mass index; MELD: Model for end-stage liver disease; TB: Total bilirubin; INR: International normalized ratio; GRWR: Graft to recipient weight ratio; RBC: Red blood cell; FFP: Fresh frozen plasma; ICU: Intensive care unit.

tion, followed by *Escherichia coli* (*n* = 6), *Staphylococcus aureus* (*n* = 4), *Bowman acinetobacter* (*n* = 4), *Hemolytic streptococcus* (*n* = 3), *Pseudomonas aeruginosa* (*n* = 2), *Burkholderia cepacia* (*n* = 1), *Acinetobacter lwoffii* (*n* = 1), *Xanthomonas maltophilia* (*n* = 1), *Haemophilus influenza* (*n* = 1), *Klebsiella pneumonia* (*n* = 1), *Enterobacter cloacae* (*n* = 1), *Leuconostoc pseudomesenteroides* (*n* = 1). The most common bacterial infective site was lung (*n* = 15), followed by abdominal cavity (*n* = 12), blood (*n* = 3). *Candida albicans* (*n* = 6) was the most common pathogen in patients with fungal infection, follow by *Saccharomycetes* (*n* = 2), *Aspergillus* (*n* = 1). Fungal infections were observed in lung in 7 patients and in gastrointestinal tract in 2 recipients.

Risk factors related to bacterial infection

As shown in Table 1, recipient age, starting albumin level < 2.8 g/dL, preoperative hyponatremia, postoperative bile leak, severe hyperglycemia, rejection and longer intensive care unit (ICU) stay were potential risk factors in univariate analysis. ROC curve analysis showed the best cut-off values for recipient age and ICU stay were 45 years and 9 d respectively (Figures 1 and 2). The corresponding are under the ROC were 0.641 and 0.680 respectively (Figures 1 and 2). When we analyzed the potential risk factors using Cox regression, only recipient age > 45 years, preoperative hyponatremia, postoperative bile leak, severe hyperglucemia and length of ICU stay > 9 d were independent risk factors for bacterial infection (Table 2).

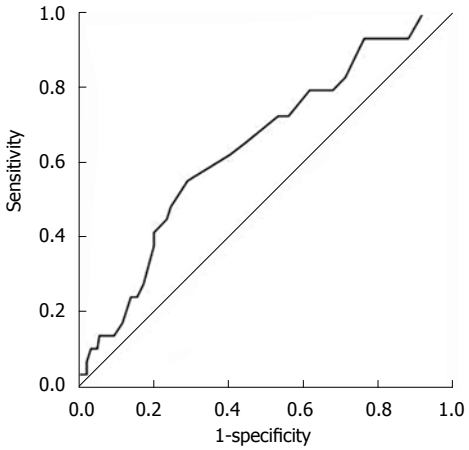

Figure 1 Receiver operating curve curve for recipient age.

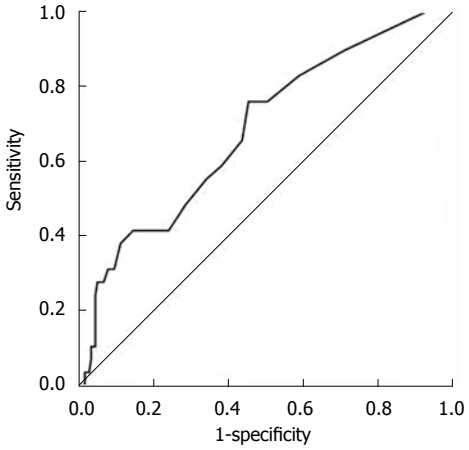

Figure 2 Receiver operating curve curve for the length of intensive care unit stay.

Risk factors related to fungal infection

As listed in Table 3, we studied the factors may be related to fungal infection using univariate analysis. Correlation testing shoed preoperative hyponatremia, massive intraoperative RBCs transfusion and postoperative bacterial infection may be contributed to postoperative fungal infection. These potential risk factors were further examined with Cox regression analysis. Only bacterial infection and massive intraoperative RBCs transfusion showed prognostic power in multivariate analysis (Table 4).

DISCUSSION

Postoperative infection is one of the most common complications in liver transplant recipients. In our current study, the incidences of bacterial and fungal infections were 14.01% and 4.35%, which were lower than previous reports[19-21]. We suggested this difference may be related to the different definition of infection. In current study, only culture-positive infections were included. Consistent with previous studies, gram-negative bacteria, especially *Enterococcus faecium* and *Escherichia coli*, were the predomi-

Table 2 Multivariate analysis for risk factors for postoperative bacterial infection

Variables	B	SE	Wald	*P* value	Exp (B)	95% CI	
						Lower	Upper
Bile leak	1.890	0.421	20.156	0.000	6.622	2.901	15.116
Hyponatremia	1.512	0.487	9.649	0.002	4.535	1.747	11.770
Hyperglycemia	1.171	0.508	5.308	0.021	3.226	1.191	8.737
ICU stay > 9 d	0.932	0.458	4.145	0.042	2.540	1.035	6.230
Recipient age > 45 yr	1.253	0.408	9.440	0.002	3.501	1.574	7.785

SE: Standard error; CI: Confidence interval; ICU: Intensive care unit.

Table 3 Univariate analysis for risk factors for postoperative fungal infection

Variables	Infected	No infected	*P* value
Donor variables			
Age (yr)	37.00 ± 7.76	34.73 ± 10.08	0.507
Gender (female)	4	74	0.739
BMI (kg/m^2)	21.64 ± 2.27	23.02 ± 2.54	0.110
Recipient variables			
Age > 45 yr	5	62	0.153
Gender (female)	1	26	0.860
BMI (kg/m^2)	21.44 ± 2.80	22.56 ± 3.16	0.295
MELD score	20.11 ± 9.35	16.23 ± 9.85	0.248
Renal dysfunction	1	15	0.698
Diabetes mellitus	0	9	0.513
Starting albumin level < 2.8 g/dL	3	39	0.391
Starting total bilirubin level	2	25	0.332
Starting INR level	1.91 ± 0.55	1.69 ± 1.43	0.650
Hyponatremia	3	16	0.010
Graft variables			
GRWR (%)	0.93 ± 0.21	0.94 ± 0.18	0.886
Intraoperative variables			
Massive RBCs transfusion	6	37	0.003
FFP transfusion > 10 units	4	45	0.220
Postoperative variables			
Bile leak	1	15	0.698
Rejection	0	5	0.629
Hyperglycemia	2	13	0.076
ICU stay > 9 d	5	98	0.748
Postoperative bacterial infection	6	23	0.000

BMI: Body mass index; MELD: Model for end-stage liver disease; INR: International normalized ratio; GRWR: Graft to recipient weight ratio; RBC: Red blood cell; FFP: Fresh frozen plasma; ICU: Intensive care unit.

nant bacterial pathogens, whereas *Candida albicans* was the most common fungal pathogen[22].

Postoperative bile leak was an independent risk factor for bacterial infection of LDLT in current study. This risk factor was not considered in some studies following deceased donor liver transplantation (DDLT)[23]. This difference was related to the low incidence of postoperative bile leak in patients underwent DDLT. However, bile leak was one of the most common complications in LDLT recipients. This factor should not be ignored in LDLT. Patients with postoperative bile leak suffered from longer abdominal drainage which may increase the risk of intraabdominal and wound infection[24]. Additionally, bile leak can cause biloma that often progress to an infected abscess[25].

Table 4 Multivariate analysis for risk factors for postoperative fungal infection

Variables	B	SE	Wald	*P* value	Exp (B)	95% CI	
						Lower	Upper
Massive RBCs transfusion	1.887	0.710	7.062	0.008	6.599	1.641	26.542
Bacterial infection	2.429	0.711	11.686	0.001	11.346	2.819	45.673

SE: Standard error; CI: Confidence interval; RBC: Red blood cell.

It was interesting that patient more than 45 years old was a risk factor related to postoperative bacterial infection. We acknowledge the cut-off value of recipient age was so young in our study. The mean recipient age in current study was 42.93 ± 8.77 years. This was a potential explanation. Similar to our results, Nayaranan *et al*[26] suggested patient's age greater than 42 years old was significantly associated with a poor long-term survival. This finding suggested the incidence of postoperative bacterial infection may be increased with the increasing of recipient age.

Preoperative diabetes mellitus didn't increase the risk of postoperative infection in our study. However, John *et al*[27] suggested pretransplant diabetes was associated with increased postoperative morbidity and mortality. Recently, Ling *et al*[28] confirmed preexisting diabetes was not a contraindication for liver transplantation. Well controlled pretransplant diabetes will not increase the risk of postoperative complication. In our practice, the nine patients with pretransplant diabetes had normal blood sugar level at the time of transplantation. Contrary to pretransplant diabetes mellitus, severe postoperative hyperglycemia was an independent risk factor for bacterial infection in current study. However, after transplantation, the administration of immunosuppressive agents, including cyclosporine, steroids and tacrolimus, may cause postoperative hyperglycemia. Ata *et al*[29] confirmed postoperative hyperglycemia was the most important risk factor for surgical site infection in general surgery patients. Rueda *et al*[30] reported hyperglycemia will increase the risk for and severity of pneumonia among non-diabetic patients.

It was easy to understand prolonged ICU stay and hyponatremia were associated with postoperative bacterial infection. Mnatzaganian *et al*[31] confirmed the incidences of bloodstream and urinary infections of patients in ICU were higher than those in regular ward. Suljagic *et al*[32] confirmed the incidence of nosocomial bloodstream infection of ICU patients was higher than non-ICU patients. Stormont *et al*[33] confirmed hyponatremia was associated with pneumonia. Zilberberg *et al*[34] suggested hyponatremia was associated with worsened clinical outcomes among patients with pneumonia.

Although the relationship between massive RBCs transfusion and bacterial infection was well established in previous studies, there were little information of the correlation of massive RBCs transfusion and fungal in-

fection. Current study suggested massive RBCs transfusion will increase the risk of fungal infection after liver transplantation. Blood transfusion can cause transfusion-related immunomodulation which will suppress the recipient's immune function[35]. However, it remains unclear why massive transfusion was not a risk factor for bacterial infection in current study.

Postoperative bacterial infection showed significantly prognostic power for fungal infection in current study. Antibiotics, especially broad-spectrum antibiotics, were administrated to patients with bacterial infection in the case of lacking culture results. Broad-spectrum antibiotics might lead to dysbacteriosis and increase fungal infection[36]. However, a recent study which was performed by Nafady-Hego *et al*[37] suggested bacterial infection was not a risk factor for fungal infection after pediatric LDLT. Younger recipient age, lower dosages of immunosuppressive agents and different infection prophylaxis might be the potential explanation for this difference.

In conclusion, preoperative hyponatremia, recipient age > 45 years, longer ICU stay, postoperative bile leak and severe hyperglycemia may be related to postoperative bacterial infection, whereas massive intraoperative RBCs transfusion and postoperative bacterial infection may lead to postoperative fungal infection. Current finding suggested postoperative bacterial and fungal infections were associated with pre-, intra- and post-operative factors.

COMMENTS

Background

Infection is a leading cause of postoperative mortality and morbidity after liver transplantation. To identify the pattern and risk factors related to postoperative bacterial and fungal infections is important to transplant surgeon.

Research frontiers

The pattern and risk factors of postoperative infections following living donor liver transplantation are not well established. This study was performed to identify the pattern and risk factors related to bacterial and fungal infections in the first 3-mo after living donor liver transplantation.

Innovations and breakthroughs

This study oultlines a comprehensive experience of 207 patients over an eight year period of infections in the first 3-mo following living donor liver transplantation. It documents the site of infection, organisms involved and the predictive risk factors.

Applications

This study could guide the clinical management of early bacterial and fungal infections after living donor liver transplantation.

Terminology

Serious infection was defined as the culture-positive bacterial or fungal infection in the blood, sputum, urine, or ascetic fluid which was obtained on the basis of clinical suspicion of an infection.

Peer review

The article is well written. The analysis of the data is sound and the conclusions reached appear valid. Overall, it significantly contributes to a relevant issue in this field and should be considered for publication.

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S- Editor Shi ZF **L- Editor** A **E- Editor** Zhang DN