Title: Pre-transplant serum procalcitonin level for prediction of early post-transplant sepsis in living donor liver transplantation

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Abstract

Aim: Infections are frequent causes of in-hospital mortality after liver transplantation (LT). Elimination of possible risks in the pre-transplant period, early diagnosis of post-transplant sepsis, and prompt administration of antimicrobial agents are important. The objectives of this study were to analyze the impact of early post-transplant sepsis on outcomes and to clarify the value of predictive factors for early post-transplant sepsis.

Methods: The study included 136 patients who underwent initial living donor LT (LDLT) at our institute from April 2009 to December 2016. Sepsis was defined using the third international consensus criteria. The results of biochemical tests at the introduction of anesthesia before LDLT were collected for pre-transplant evaluation.

Results: Post-transplant sepsis was found in 37 patients (27.2%). More patients had a pre-transplant serum procalcitonin (PCT) level >0.5 ng/ml in the sepsis group than in the non-sepsis group (11 [29.7%] vs. 10 [10.1%]; P=0.007). The 1-year survival rates in the sepsis group were significantly lower than those in the non-sepsis group (53.8% vs. 87.2%; P <0.001). Multivariate analysis identified pre-transplant serum PCT >0.5 ng/ml (odds ratio 3.8, 95%

confidence interval 1.3-10.9; P=0.01) as the only independent risk factor for

post-transplant sepsis.

Conclusions: Survival of patients with early post-transplant sepsis was poor

and the incidence of sepsis was associated with the pre-transplant serum PCT

level. Re-evaluation of the general condition and rescheduling of LT are

considered in a patient with pre-transplant serum PCT >0.5 ng/ml.

Key words: infection, liver transplantation, living donor, procalcitonin

Introduction

Infections are a frequent cause of in-hospital mortality after liver

transplantation (LT) [1, 2]. These complications are mostly observed during the

first month after LT [3]. Post-transplant infection requiring cardiopulmonary

support or renal replacement therapy (RRT), such as sepsis and septic shock, is

particularly associated with poorer outcomes [4, 5]. Early recognition of an

altered condition, early diagnosis, and prompt administration of antimicrobial

agents in the post-transplant period are essential for improvement of post-

transplant outcomes. However, accurate and timely diagnosis of sepsis may be

difficult due to impaired consciousness after major surgery, immunosuppression

therapy, and possible rejection [6, 7]. In addition, results from microbiological

cultures can only be obtained after clinical signs of sepsis appear. Serum

procalcitonin (PCT) is used as a biomarker of bacterial infection and sepsis in a

number of areas, and may be useful for early detection of infection and

differentiation from non-infectious complications after LT [6, 8, 9]. However, it is

difficult to exclude the effects of highly invasive surgical procedures and post-

transplant immunosuppression therapy on the serum PCT level [10].

Another strategy to improve outcomes is recognizing and eliminating the

predictors for post-transplant sepsis during the pre-transplant period and transplant surgery. This strategy is feasible, especially in LDLT, because this surgery is usually performed in an elective manner. The objectives of this study were to analyze the impact of early post-transplant sepsis on outcomes and to identify predictive factors for this condition.

Methods

Patients

We retrospectively analyzed 136 adult patients who underwent initial LDLT at Nagasaki University Hospital from April 2009 to December 2016. The indications for LT were liver cirrhosis due to hepatitis C virus infection (n=56, 41.2%), alcoholic liver cirrhosis (n=19, 14.0%), liver cirrhosis due to hepatitis B virus infection (n=16, 11.8%), primary biliary cirrhosis (n=15, 11.0%), cryptogenic liver cirrhosis (n=12, 8.8%), acute liver failure (n=7, 5.1%), primary sclerosing cholangitis (n=4, 2.9%), Caroli disease (n=2, 1.5%), and other diseases (n=5, 3.7%). All transplantations were approved by the ethics committee of Nagasaki University Hospital.

Definitions of infection and sepsis

Bacterial infections occurring prior to LDLT that required intravenous antimicrobial treatment during the same hospital stay were defined as pre-transplant infections. Infections were defined using the criteria proposed by the Centers for Disease Control and Prevention and as reported in LT recipients [11]. Patients with pre-transplant infections underwent LDLT after confirmation of improved general condition, negative cultures, and appropriate biochemical test results. Post-transplant sepsis was defined as life-threatening organ dysfunction consequent to the infection, according to the third international consensus definitions for sepsis and septic shock (Sepsis-3). Organ dysfunction was identified as an acute change in total Sequential Organ Failure Assessment (SOFA) score ≥ 2 points [12]. Sepsis occurring within one month after LDLT was defined as early post-transplant sepsis in this study.

Biochemical examination

The WBC count and CRP level immediately before LDLT were investigated for pre-transplant evaluation. This was because the day of LDLT is the latest timing

to evaluate pre-transplant condition in the retrospective study. The institutional

upper normal limits of WBC and CRP are 8,600 /µl and 0.5 mg/dl, respectively.

In addition, we routinely collect and storage blood sample at this time point.

Serum PCT levels were retrospectively measured using this storage sample. The

upper normal limit of PCT was 0.5 ng/ml.

Surgical procedures and perioperative management

   We selected the left lobe graft with the middle hepatic vein when the ratio of

graft volume to recipient standard liver volume (GV/SLV) was >30%. A right

lobe graft was an alternative if the left lobe was not feasible for donation. The

ratio was calculated from the results of a volumetric study using computed

tomography. Arterial reconstructions were carried out under a microscope using

end-to-end anastomosis with interrupted suture techniques [13]. Duct-to-duct

anastomosis was performed for biliary reconstruction, except in patients with

primary sclerosing cholangitis. A biliary splint (2 mm, vinyl chloride tube) was

placed beyond the anastomosis and the splint was externalized through the

upper edge of the duodenum with a Witzel-type fistula. The splint was removed

about three months after LDLT using a two-step protocol [14].

Antimicrobial prophylaxis consisted of cefotaxime (4 g/day) and ampicillin (4 g/day). These drugs were injected 30 min before laparotomy and continued up to 48 h after LDLT. If the patient had pre-transplant infection within 2 weeks prior to LDLT, their antimicrobial therapy was continued perioperatively. Prophylactic valganciclovir (10 mg/kg/day) was given for 14 days when anti-cytomegalovirus immunoglobulin G was positive in the donor and negative in the recipient; trimethoprim-sulfamethoxazole (1 g daily) was administered for Pneumocystis jirovecii pneumonia prophylaxis for 3 months [15]. Early nutritional therapy was administered to all recipients via tube jejunostomy or nasojejunal feeding tube from the day of LDLT to the day when the recipient could eat sufficiently. A Central venous triple-lumen catheter was inserted from right internal juggler vein after induction of anesthesia. If the patient already had central venous catheter (CVC) preoperatively, anesthesiologists replace the existing line with a new one from different place. We usually remove CVC after withdrawal of continuous venous administration of vasopressors and diuretic drugs and then change to peripheral intravenous infusion.

Immunosuppression therapy

In ABO-incompatible LDLT cases, we use rituximab (375 mg/m^2) as an

induction 10-14 days before LDLT. The standard immunosuppression regimen

comprised tacrolimus and steroids. The steroid were gradually tapered and

discontinued by three months after LDLT. The target trough levels of tacrolimus

were 10-15 ng/ml. Mycophenolate mofetil was added for ABO-incompatible

LDLT cases and patients in whom trough levels of tacrolimus were intentionally

kept lower due to renal dysfunction [16]. In the present study, 95 patients

(69.9%) received Mycophenolate mofetil.

Statistical analysis

IBM SPSS Statistics 21 (SPSS, Inc., Chicago, IL) was used for statistical

analysis. A Mann-Whitney U test was used to analyze continuous data, and a

chi-square test was used for categorical data. Overall survival was calculated

using the Kaplan-Meier method, and data were compared by log-rank test.

Logistic regression analysis was used to assess risk factors for early post-

transplant sepsis. Continuous data were dichotomized using the median. Factors

with p ≤0.10 in univariate analysis were evaluated as potential risk factors in

multivariate analysis. P <0.05 was considered to be significant in all analyses.

Results

Patient characteristics

The characteristics of the 136 patients (75 males and 61 females) are

summarized in Table 1. The median [range] recipient age was 59 [17-72] years

old, the model for end-stage liver disease (MELD) score was 16 [7-47], and the

Child-Pugh score was 10 [5-15]. Pre-transplant infections were observed in 37

patients (27.2%). In detail, 17 urinary tract infection, 6 biliary infection, 5

pneumonia, 4 bacteremia, and 3 spontaneous bacterial peritonitis were

observed respectively. Two patients acquired systemic infection without positive

cultures were received empirical antimicrobial therapy. Ten patients (7.4%)

were admitted to the intensive care unit until LDLT due to 5 acute liver failure

and 5 acute on chronic liver disease. Eight (5.9%) patients were on dialysis.

Increased WBC count were observed in 9 patients. Serum CRP >0.5 ng/ml was

present in 47 patients (34.6%), and the serum PCT >0.5 ng/ml was present in

21 patients (15.4%). The median GV/SLV ratio was 46.0% [25.9-75.0]. Duct-to-

duct biliary anastomosis was performed in 127 cases (93.4%) and splenectomy

was performed in 80 (58.8%). The median operative time was 775 [510-1,384]

minutes and the median blood loss was 6.2 [0.5-52.0] L. The median amount of

red cell concentrates (RCC) transfusion was 13 [0-96] units.

Early post-transplant sepsis

   Post-transplant sepsis occurred in 37 of 136 patients (27.2%), and these

patients had a significantly greater blood loss (7.8 [1.9-52.0] vs. 5.5 [0.5-37.0]

L; P=0.02) and greater amount of RCC transfusion (18 [0-72] vs. 12 [0-96]

units; P=0.03) compared with the non-sepsis group. Pre-transplant serum PCT

>0.5 ng/ml (11 [29.7%] vs. 10 [10.1%]; P=0.007) were more frequent in the

sepsis group, but the incidence of increased WBC count and CRP levels did not

differ markedly between the groups. Higher MELD score (18 [7-47] vs. 15 [7-

39]; P=0.07) and higher rate of pre-transplant infections (14 [37.8%] vs. 23

[23.2%]; P=0.07) were observed in post-transplant sepsis group but not

statistically significant.

   In post-transplant sepsis group, their median SOFA score was 14 [4-18] at

the time of diagnosis. The difference between their baseline SOFA, 24 hours

before diagnosis of sepsis and at the time of diagnosis was 4 [2-10]. The

sources of post-transplant sepsis and the causative bacterial pathogens are

shown in Table 2. Among the 37 patients with post-transplant sepsis, 5 (13.5%)

were diagnosed with sepsis without positive cultures. All of these episodes

occurred within 2 weeks after surgery. Fourteen patients had multiple infectious

sites. The sources of sepsis were identified as bacteremia (n=19), pulmonary

infection (n=13), intra-abdominal infection (n=6), urinary tract infection (n=5),

and biliary infection (n=4). Histopathologically proven acute cellular rejection

was observed in 9 patients (6.6%). Since elevation of their SOFA score was not

resulted from infection, they were not included in early post-transplant sepsis

group.

Patient outcomes

   The 1-year survival rates was 87.2% in the non-sepsis group, and 53.8% in

the sepsis group, with significantly worse survival in the sepsis group (*P*

<0.001) (Figure 1). We divided the patients with post-transplant sepsis into 2

groups, the patients with SOFA ≥15 and the patient with SOFA ≤14 according

to the Receiver Operating Characteristic curves. The 1-year survival rate of

patient with SOFA ≥15 at the time of diagnosis of sepsis was significantly poor

compared to the patient with SOFA ≤14 (23.5% vs. 79.7%; p <0.001).

Risk factors for early post-transplant sepsis

The results of univariate and multivariate analyses for early post-transplant sepsis are shown in Table 3. Pre-transplant bacterial infection (OR 2.0, 95% CI 0.9-4.5; P =0.09), pre-transplant serum PCT >0.5 ng/ml (OR 3.8, 95% CI 1.4-9.8; P =0.007), intraoperative blood loss ≥6.2 L (OR 2.6, 95% CI 1.2-5.8; P =0.02) and intraoperative RCC transfusion ≥13 units (OR 2.3, 95% CI 1.1-5.0; P =0.04) were potential risk factors in univariate analysis. In a multivariate logistic regression model, pre-transplant serum PCT >0.5 ng/ml (OR 3.8, 95% CI 1.3-10.9; P =0.01) was the only independent risk factor for post-transplant sepsis.

Characteristics of patients with pre-transplant serum PCT >0.5 ng/ml

To clarify the background of patients with pre-transplant serum PCT >0.5 ng/ml, we have compared pre-transplant characteristics of the patients. Twenty-one of 136 patients (15.4%) present pre-transplant serum PCT >0.5 ng/ml. The increase of PCT was associated with that of WBC count and CRP level. Higher

MELD score (28 [9-47] vs. 15 [7-39]; P <0.001), Higher rate of pre-transplant

infections (57.1% vs. 21.7%; P=0.002), pre-transplant ICU admission (23.8%

vs. 4.3%; P=0.008), and pre-transplant renal replacement therapy (23.8% vs.

3.5%; P=0.002) were observed in patients with PCT >0.5 ng/ml (Table 4). One-

year survival rates of patients with pre-transplant serum PCT >0.5 ng/ml and

PCT ≤0.5 ng/ml were shown in Figure 2. There were no significant difference

between the groups (69.7% vs. 80.6%; P=0.40). Among the patients with pre-

transplant PCT >0.5 ng/ml, six patients accidentally showed PCT >2.0 ng/ml

that normally interpreted as highly suspicious of systemic infection. The 1 year

survival rate of these patients was significantly worse than that of others

(20.8% vs. 80.3%; P=0.002).

Discussion

   In this study, we found an incidence of early post-transplant sepsis of 27.2%

that was associated with poorer outcomes. Survival rate in the patient with

SOFA ≥15 at the time of diagnosis of sepsis was specifically deteriorated. The

main causes of post-transplant sepsis were blood stream and respiratory

infections that may be associated with mechanical ventilation, prolonged

immobility, and long-term catheterization.

Formerly, sepsis was defined as a systemic inflammatory response caused by

known or suspected infections, and the incidence of post-transplant sepsis has

been reported as 13-46% [2, 4, 5, 17]. The outcomes of patients with post-

transplant sepsis have been extremely poor, as in our results [4, 5]. A recent

change in the definition of sepsis, using SOFA score to a focus on life-

threatening organ dysfunction might allow earlier differentiation between severe

infection and postoperative systemic inflammation. Since early recognition and

intervention in post-transplant infection is essential for improving patient's

outcome, this new definition might be reasonable. However, preventing post-

transplant sepsis is still challenging due to vulnerable patient conditions caused

by highly invasive surgery, immunosuppression therapy, and malnutrition. For

this reason, we focused on pre-transplant and surgical factors to exclude the

possible predictors of post-transplant sepsis in scheduled LDLT.

Previous reports have identified ABO incompatibility, impaired kidney

function, Child-Pugh class C, older donor, and massive bleeding as risk factors

for post-transplant infections and sepsis [17-19]. In contrast, the pre-transplant

PCT level was the only independent risk factor found in the present study. To

the best of our knowledge, this is the first report that emphasizes the impact of

the pre-transplant PCT level on post-transplant sepsis. PCT is the pro-peptide

precursor of calcitonin, is composed of 116 amino acids, and is mainly produced

by the thyroid gland [20]. In an inflammatory setting, PCT is also released from

peripheral blood monocytes, macrophages, lung, kidney, pancreas, adrenal

grand, and liver [6, 8, 10, 21], and is an accurate marker for diagnosis, severity,

and follow-up of infection and sepsis in different patient groups [20, 22, 23]. In

a post-transplant setting, studies have shown the benefit of PCT for diagnosis of

bacterial infection and differentiation from acute cellular rejection [6, 8, 9].

However, the influences of the length of surgery and immunosuppression

therapy have not been sufficiently examined [10]. In this study, we focused on

the relationship between post-transplant sepsis and pre-transplant PCT that was

unaffected by surgical factors or post-transplant management.

 We note several limitations of the study. First, though the trend of elevated

PCT levels were found in patients with higher MELD score, with pre-transplant

RRT, and with history of pre-transplant bacterial infection, the causes of

elevated pre-transplant PCT levels are not completely clear and could not be

determined. Our hypothesis are elevation of PCT level might reflect insufficient recovery from pre-transplant infection or latent systemic infection without clear symptoms. Sun et al. found pre-transplant infection in 32% of DDLT patients, and reported that pre-transplant infections did not affect outcomes if these infections were adequately treated [24]. The patients with pre-transplant infections in our center were treated with appropriate antimicrobial therapy and then underwent LDLT after confirmation of improved general condition, negative cultures, and improvement tendency of biochemical test. Under this protocol, our previous study indicated similar results in a LDLT population [25]. In addition, since the detected pathogens during pre-transplant period were not found after LDLT in any of the patients, pre-transplant bacterial infection thought to be treated sufficiently [25]. However, according to the result of present study, now we think judgment of adequate healing and proper timing of LT need amendment. We anticipate that measurement of pre-transplant serum PCT might become a new benchmark for prediction of the extent of recovery from pre-transplant infection. The trend of PCT level during pre-transplant period may also essential to clarify the patient condition. We will evaluate this point prospectively in the future study.

Second, the clinical relevance and cutoff value for serum PCT in patients with RRT are uncertain because higher serum PCT levels that decreased after dialysis have been found in patients with reduced renal function [26, 27]. This suggests that the pre-transplant PCT level prior to RRT might be overestimated. In fact, the rate of pre-transplant PCT >0.5 ng/ml, the only independent predictive factor of early post-transplant sepsis was significantly higher in patients with pre-transplant RRT despite RRT was not associated with the occurrence of early post-transplant sepsis. However, though the adequate cutoff value for PCT in patients with RRT is under debate, aggressive pre-transplant evaluation of patients with reduced renal function is essential since they are reported more susceptible to perioperative complications even in elective liver surgery [28].

Based on the results of this study, we are now measuring pre-transplant serum PCT levels in all LDLT recipients on a regular basis from their admission day. Upward trend of PCT with higher than 0.5 ng/ml are regarded as relative contraindications for LDLT. Rescheduling of LT should be considered in such cases because these patients require close observation or preemptive treatment for pre-transplant infection, even if systemic symptoms are absent. This new

strategy will be evaluated in a prospective study to examine associations among

pre-transplant PCT level, recovery from pre-transplant infection, and latent

systemic infection.

   In conclusion, survival of patients with early post-transplant sepsis was poor,

and pre-transplant serum PCT was a useful biomarker for prediction of this

complication. Since LDLT is usually performed as an elective surgery,

rescheduling of transplantation and evaluation of pre-transplant infection should

be considered, regardless of systemic symptoms, in patients with pre-transplant

serum PCT >0.5 ng/ml.

References

1.   Kaido T, Egawa H, Tsuji H et al. In-hospital mortality in adult recipients of living donor liver transplantation: experience of 576 consecutive cases at a single center. Liver Transpl 2009; 15: 1420-1425.

2.   Saner FH, Olde Damink SW, Pavlakovic G et al. Pulmonary and blood stream infections in adult living donor and cadaveric liver transplant patients. Transplantation 2008; 85: 1564-1568.

3.   Garbino J, Romand JA, Pittet D et al. Infection and rejection in liver transplant patients: a 10-year Swiss single-centre experience. Swiss Med Wkly 2005; 135: 587-593.

4.   Ikegami T, Shirabe K, Yoshiya S et al. Bacterial sepsis after living donor liver transplantation: the impact of early enteral nutrition. J Am Coll Surg 2012; 214: 288-295.

5.   Takeda K, Sawada Y, Kumamoto T et al. Severe Sepsis After Living Donor Liver Transplantation: Risk Factors and Outcomes. Transplant Proc 2016; 48: 2124-2129.

6.   Kaido T, Ogawa K, Fujimoto Y et al. Perioperative changes of procalcitonin levels in patients undergoing liver transplantation. Transpl Infect Dis 2014; 16:

790-796.

7.   van den Broek MA, Olde Damink SW, Winkens B et al. Procalcitonin as a

prognostic marker for infectious complications in liver transplant recipients in an

intensive care unit. Liver Transpl 2010; 16: 402-410.

8.   Perrakis A, Stirkat F, Croner RS et al. Prognostic and diagnostic value of

procalcitonin in the post-transplant setting after liver transplantation. Arch Med

Sci 2016; 12: 372-379.

9.   Kuse ER, Langefeld I, Jaeger K, Kulpmann WR. Procalcitonin in fever of

unknown origin after liver transplantation: a variable to differentiate acute

rejection from infection. Crit Care Med 2000; 28: 555-559.

10.   Sandkovsky U, Kalil AC, Florescu DF. The use and value of procalcitonin

in solid organ transplantation. Clin Transplant 2015; 29: 689-696.

11.   Garner JS, Jarvis WR, Emori TG et al. CDC definitions for nosocomial

infections, 1988. Am J Infect Control 1988; 16: 128-140.

12.   Singer M, Deutschman CS, Seymour CW et al. The Third International

Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama 2016; 315:

801-810.

13.   Takatsuki M, Chiang YC, Lin TS et al. Anatomical and technical aspects of

hepatic artery reconstruction in living donor liver transplantation. Surgery 2006; 140: 824-828; discussion 829.

14.   Eguchi S, Takatsuki M, Hidaka M et al. Two-step biliary external stent removal after living donor liver transplantation. Transpl Int 2008; 21: 531-533.

15.   Hara T, Soyama A, Hidaka M et al. Analysis of early relaparotomy following living donor liver transplantation. Liver Transpl 2016; 22: 1519-1525.

16.   Takatsuki M, Soyama A, Muraoka I et al. Post-operative complications requiring hospitalization more than one yr after living donor liver transplantation. Clin Transplant 2014; 28: 105-110.

17.   Iida T, Kaido T, Yagi S et al. Posttransplant bacteremia in adult living donor liver transplant recipients. Liver Transpl 2010; 16: 1379-1385.

18.   Kim YJ, Kim SI, Wie SH et al. Infectious complications in living-donor liver transplant recipients: a 9-year single-center experience. Transpl Infect Dis 2008; 10: 316-324.

19.   Kaido T, Mori A, Ogura Y et al. Pre- and perioperative factors affecting infection after living donor liver transplantation. Nutrition 2012; 28: 1104-1108.

20.   Assicot M, Gendrel D, Carsin H et al. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993; 341: 515-518.

21.   Brunkhorst FM, Heinz U, Forycki ZF. Kinetics of procalcitonin in iatrogenic

sepsis. Intensive Care Med 1998; 24: 888-889.

22.   Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for

sepsis diagnosis in critically ill patients: systematic review and meta-analysis.

Lancet Infect Dis 2007; 7: 210-217.

23.   Uzzan B, Cohen R, Nicolas P et al. Procalcitonin as a diagnostic test for

sepsis in critically ill adults and after surgery or trauma: a systematic review and

meta-analysis. Crit Care Med 2006; 34: 1996-2003.

24.   Sun HY, Cacciarelli TV, Singh N. Impact of pretransplant infections on

clinical outcomes of liver transplant recipients. Liver Transpl 2010; 16: 222-228.

25.   Hara T, Soyama A, Takatsuki M et al. The impact of treated bacterial

infections within one month before living donor liver transplantation in adults.

Ann Transplant 2014; 19: 674-679.

26.   Herget-Rosenthal S, Marggraf G, Pietruck F et al. Procalcitonin for

accurate detection of infection in haemodialysis. Nephrol Dial Transplant 2001;

16: 975-979.

27.   Dahaba AA, Rehak PH, List WF. Procalcitonin and C-reactive protein

plasma concentrations in nonseptic uremic patients undergoing hemodialysis.

Intensive Care Med 2003; 29: 579-583.

28.   Squires MH, 3rd, Lad NL, Fisher SB et al. The effect of preoperative renal

insufficiency on postoperative outcomes after major hepatectomy: a multi-

institutional analysis of 1,170 patients. J Am Coll Surg 2014; 219: 914-922.

Figure Legend

Figure 1. One-year survival rates of patients with and without post-transplant sepsis. The survival rates after LDLT were significantly lower in patients with post-transplant sepsis (53.8% vs. 87.2%; P <0.001).

Figure 2. One-year survival rates of patients with pre-transplant serum PCT >0.5 ng/ml and PCT ≤0.5 ng/ml. There were no significant difference between the groups (69.7% vs. 80.6%; P=0.40).

Table 1. Patient characteristics

Valuables	Total n=136	Early post-transplant sepsis		P value
		(+) n=37	(-) n=99	
Recipient Age, y	59 (17-72)	59 (17-71)	57 (24-72)	0.544
Recipient Sex, male	75 (55.1%)	18 (48.6%)	57 (57.6%)	0.230
Donor Age, y	38 (20-65)	40 (20 - 63)	36 (20 - 65)	0.557
MELD score	16 (7-47)	18 (7-47)	15 (7-39)	0.068
Child-Pugh score	10 (5-15)	10 (5 – 14)	10 (5 – 15)	0.801
HCV infection	57 (41.9%)	12 (32.4%)	45 (45.5%)	0.120
Graft type LL /RL /RLS	85 /49 /2 (62.5 /36.0 /1.5%)	27 /10 /0 (73.0 /27.0 /0%)	58 / 39 /2 (58.6 /39.4 /2.0%)	0.249
Pre-transplant bacterial infection	37 (27.2%)	14 (37.8%)	23 (23.2%)	0.070
Pre-transplant ICU admission	10 (7.4%)	4 (10.8%)	6 (6.1%)	0.272
Pre-transplant RRT	8 (5.9%)	4 (10.8%)	4 (4.0%)	0.140
WBC>8,600/µl (Day0, before LT)	9 (6.6%)	4 (10.8%)	5 (5.1%)	0.203
CRP>0.5 mg/dl (Day0, before LT)	47 (34.6%)	16 (43.2%)	31 (31.3%)	0.136
PCT>0.5 ng/ml (Day0, before LT)	21 (15.4%)	11 (29.7%)	10 (10.1%)	0.007
ABO incompatible	27 (19.9%)	8 (21.6%)	19 (19.2%)	0.461
GV/SLV, %	46.0 (25.9-75.0)	44.3 (28.9-66.5)	46.1 (25.9-75.0)	0.184
Hepaticojejunostomy	9 (6.6%)	2 (5.4%)	7 (7.1%)	0.537
Splenectomy	80 (58.8%)	19 (51.4%)	61 (61.6%)	0.187
Operative time, minutes	775 (510-1,384)	819 (578-1,253)	761 (510-1,384)	0.137
Blood loss, L	6.2 (0.5-52.0)	7.8 (1.9-52.0)	5.5 (0.5-37.0)	0.024
RCC transfusion, units	13 (0-96)	18 (0-72)	12 (0-96)	0.025

Data are represented as n (%) or median (range).

MELD, model for end-stage liver disease; HCV, hepatitis virus C; LL, left lobe graft; RL, right lobe graft; RLS, right lateral segment graft; LT, liver transplantation; RRT, renal replacement therapy; WBC, white blood cells; CRP, C-reactive protein; PCT, procalcirtonin; GV/SLV, graft volume per recipient's standard liver volume; RCC, red cell concentrates

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Table 2. Culture results and detected pathogens in patients with post-transplant sepsis

Pathogens	- 1 week	1-2 weeks	2-4 weeks
Blood, n=19	9	5	5
Pseudomonas aeruginosa	4	3	1
Enterococcus faecium	3	1	
Enterobacter cloacae	1	1	1
Escherichia coli	1		1
Klebsiella pneumoniae			2
Sputum, n=13	8	4	1
MRSA	2		
Pseudomonas aeruginosa	2	1	1
Stenotrophomonas maltophilia	1	2	
Enterobacter cloacae	1	1	
Staphylococcus epidermidis	1		
MSSA	1		
Escherichia coli			
Ascites, n=6	2	4	0
Pseudomonas aeruginosa	2	2	
Enterococcus faecium		1	
Enterococcus faecalis		1	
Urine, n=5	2	0	3
Pseudomonas aeruginosa	1		2
Escherichia coli	1		
Enterobacter cloacae			1
Bile, n=4	1	0	3
Enterococcus faecium	1		1
Enterobacter cloacae			1
Escherichia coli			1
Undetected, n=5	4	1	0

MRSA, Methicillin-resistant Staphylococcus aureus; MSSA, Methicillin-sensitive Staphylococcus aureus

Data are overlapping.

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Table 3.   Risk factors for early post-transplant sepsis

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age ≥60 y	1.063	0.498 – 2.268	0.876			
MELD score ≥20	1.364	0.626 – 2.969	0.435			
Child Pugh score ≥10	1.023	0.470 – 2.228	0.954			
HCV infection	0.576	0.260 – 1.274	0.173			
Pre-transplant bacterial infection	2.011	0.893 – 4.529	0.092	1.326	0.536 – 3.279	0.542
Pre-transplant ICU stay	1.879	0.499 – 7.076	0.351			
Pre-transplant RRT	2.879	0.681 – 12.167	0.150			
WBC>8,600/µl (Day0, before LT)	2.279	0.577 – 8.997	0.240			
CRP>0.5 mg/dl (Day0, before LT)	1.671	0.769 – 3.634	0.195			
PCT >0.5 ng/ml (Day0, before LT)	3.765	1.440 – 9.848	0.007	3.767	1.306 – 10.866	0.014
ABO incompatible	1.162	0.459 – 2.941	0.752			
GV/SLV <35%	1.250	0.403 – 3.877	0.699			
Hepaticojejunostomy	0.751	0.149 – 3.791	0.729			
Splenectomy	0.658	0.307 – 1.408	0.280			
Operative time ≥13 hours	1.512	0.707 – 3.237	0.287			
Blood loss ≥6.2 L	2.604	1.177 – 5.763	0.018	3.587	0.741 – 17.363	0.112
RCC transfusion ≥13 unit	2.308	1.055 – 5.048	0.036	0.698	0.147-3.317	0.651

OR, odds ratio; CI, Confidential interval; MELD, model for end-stage liver disease; HCV, hepatitis virus C; LT, liver transplantation; RRT, renal replacement therapy; WBC, white blood cells; CRP, C-reactive protein; PCT, procalcirtonin; GVSLV, graft volume per recipient's standard liver volume; RCC, red cell concentrates
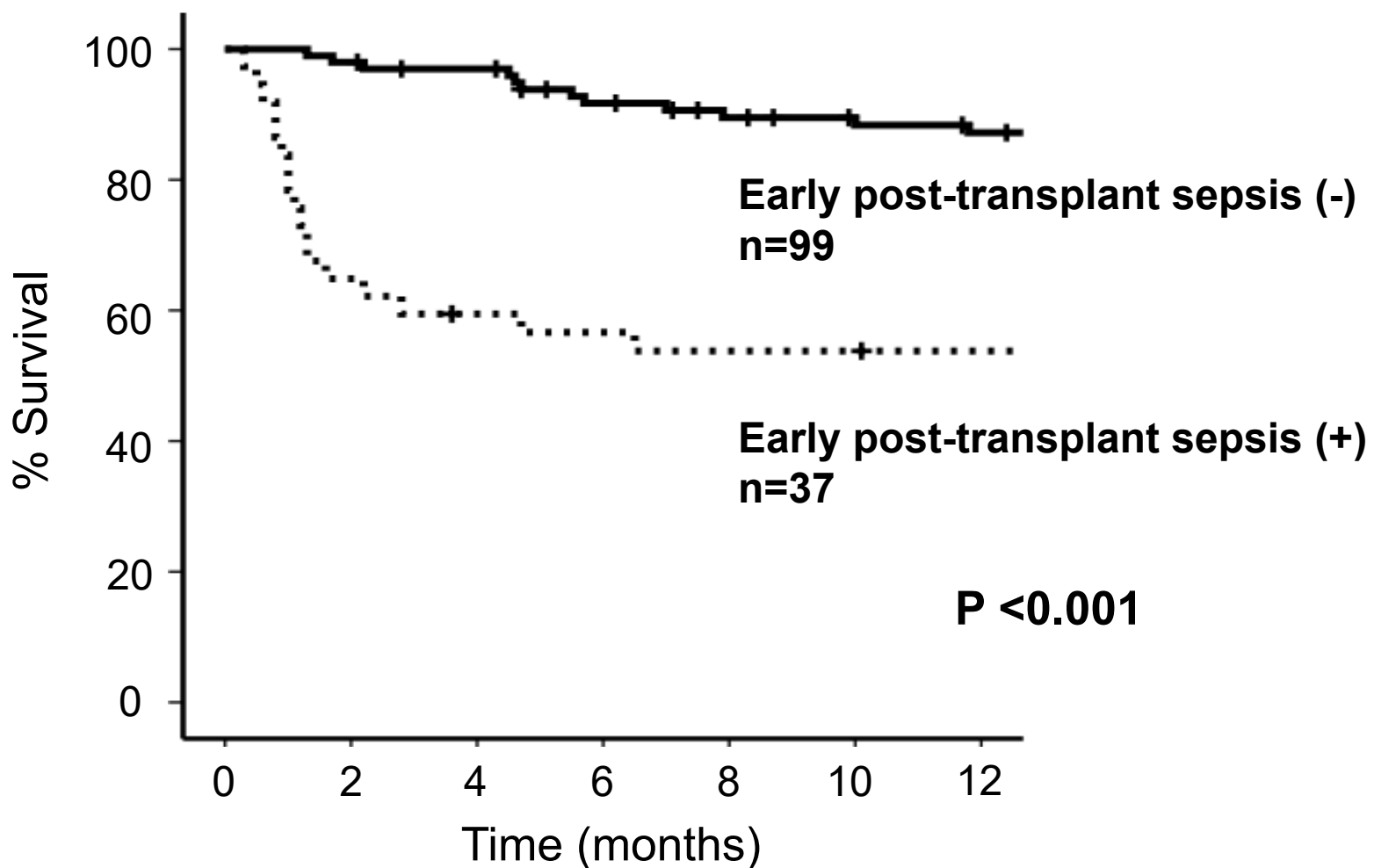
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Table 4. Characteristics of patients with pre-transplant PCT >0.5 ng/ml

Pre-transplant valuables	Pre-transplant PCT level		*P*-value
	≤0.5, n=115	>0.5, n=21	
Recipient Age, y	59 (24-72)	55 (17-67)	0.054
Recipient Sex, male	65 (56.5%)	10 (47.6%)	0.302
MELD score	15 (7-39)	28 (9-47)	<0.001
HCV infection	50 (43.5%)	7 (33.3%)	0.268
Pre-transplant bacterial infection	25 (21.7%)	12 (57.1%)	0.002
Pre-transplant ICU admission	5 (4.3%)	5 (23.8%)	0.008
Pre-transplant RRT	3 (2.6%)	5 (23.8%)	0.002
WBC >8,600/μl	4 (3.5%)	5 (23.8%)	0.005
CRP >0.5 mg/dl	31 (27.0%)	16 (76.2%)	<0.001
ABO incompatible	23 (20.0%)	4 (19.0%)	0.594

Data are represented as n (%) or median (range).

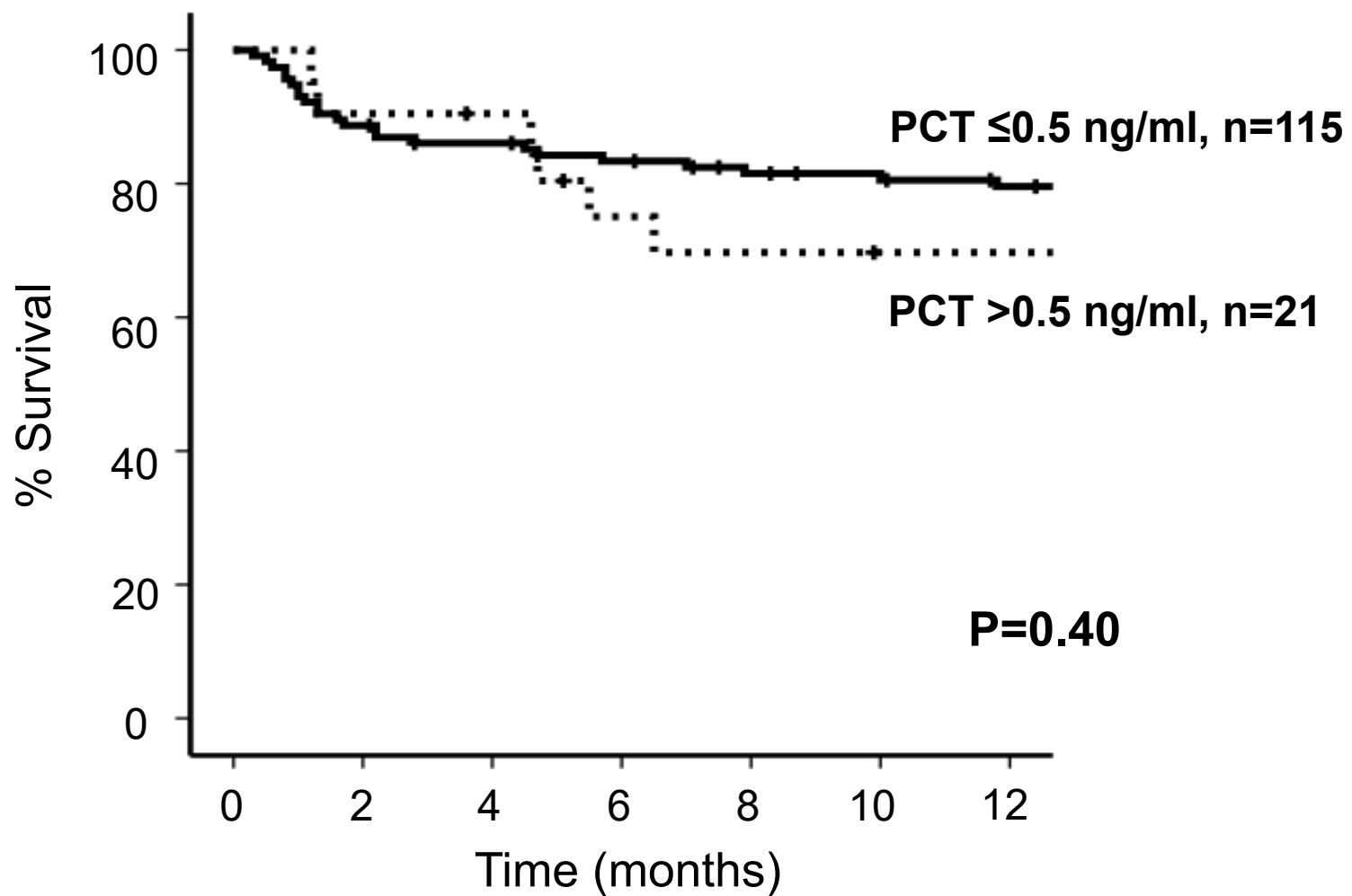MELD, model for end-stage liver disease; HCV, hepatitis virus C; RRT, renal replacement therapy

Figure 1

Figure 2