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ORIGINAL ARTICLE

Decreased graft survival in liver transplant recipients of donors with positive blood cultures: a review of the United Network for Organ Sharing dataset

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SUMMARY

Liver transplantation using blood culture positive donors (BCPD) has allowed a significant expansion of the donor pool. We aimed to characterize BCPD and assess the outcomes of BCPD liver transplant recipients. We retrieved data from the United Network for Organ Sharing (UNOS) registry on all adults who underwent primary, single-organ deceased-donor liver transplantation in the USA between 2008 and 2013. Patients were classified into two cohorts: the BCPD cohort and the non-BCPD cohort. One-year graft and patient survival were compared between cohorts using Kaplan–Meier estimates and Cox models. A total of 28 961 patients were included. There were 2316 (8.0%) recipients of BCPD. BCPD were more likely to be older, female, black, diabetic, hypertensive, and obese compared to non-BCPD. Graft survival was significantly lower in BCPD recipients compared to non-BCPD recipients (Kaplan–Meier, 0.85 vs. 0.87; $P = 0.009$). Results remained significant in propensity-matched analysis ($P = 0.038$). BCPD was independently associated with decreased graft survival (adjusted HR; 1.10, 95% CI 1.01–1.20; $P = 0.04$). There were no significant differences in patient survival between study groups. BCPD was associated with decreased graft survival in liver transplant recipients. Studies are needed to identify subgroups of BCPD with the highest risk of graft failure and characterize the underlying pathogenic mechanisms.

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Key words
donor bacteremia, graft survival, infection, liver transplant, outcome, patient survival

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Introduction

The disparity between liver allograft supply and demand continues to increase worldwide. In 2013, 5710 adults received a deceased-donor liver transplant in the USA, whereas 15 027 candidates were registered on the liver transplant waiting list by the end of that same year [1].

The use of blood culture positive donors (BCPD) has significantly increased the donor pool. It has been estimated that at least 5% of donors have bacteremia at time of organ procurement [2]. The overall experience using bacteremic donors has shown no significant effects on graft and patient survival, and the rates of infection transmission from donors to recipients have

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been reported to be low [3–6]. However, most of the previous published experience on recipients of BCPD comes from single-center studies that may have failed to detect differences in outcomes possibly related to the lack of statistical power.

The United Network for Organ Sharing (UNOS) collects information on clinical infections confirmed by positive blood cultures in donors [7]. This offers a unique opportunity to study the outcomes of liver transplant recipients of BCPD nationwide. The aim of this study was to characterize BPCD and assess the outcomes of liver transplant recipients of BCPD in comparison with non-BCPD patients.

Methods

We queried data from the UNOS registry on all adults who underwent primary, single-organ deceased-donor liver transplantation in the USA between 2008 and 2013. The UNOS registry contains de-identified data on all allografts transplanted within the USA, including information from donors and recipients. We established two cohorts according to whether patients received an allograft from BCPD prior to organ procurement, as recorded in the UNOS deceased-donor registration worksheet [7]. There were three separate and sequential items in this worksheet that were used to define BCPD: (i) presence of clinical infection on the donor (yes, no, or unknown); (ii) source of infection (blood, lung, urine, or other); and (iii) confirmed by culture (yes or no). Donors who had a clinical infection ("yes" in the first item) with a blood source ("blood" in the second item) confirmed by culture ("yes" in the third item) were defined as BCPD, similar to prior studies [8,9]. Thus, the BCPD cohort included patients who received a liver allograft from BCPD. The non-BCPD cohort included those who received a liver allograft from non-BCPD. Data on sociodemographic and clinical characteristics of donors and recipients in the two cohorts were retrieved. The chi-square and Mann–Whitney tests were used to compare categorical and continuous variables between cohorts, respectively. We also calculated standardized differences for each variable.

Patient and graft survival were estimated by using the Kaplan–Meier method. The log-rank test was used to compare differences in survival. Cox proportional hazard model was used to assess factors associated with graft survival (noncensored for death) and patient survival. The results of the Cox models were presented as adjusted hazard ratios (HR) accompanied by 95% confidence intervals (CI).

Because of significant differences in baseline characteristics of the BCPD and non-BCPD cohorts, we used propensity scores for 1:1 matching of BCPD and non-BCPD patients. All variables that were significantly different between BCPD and non-BCPD patients in the bivariate analysis as well as variables available in the UNOS dataset that could affect graft and patient survival were included to calculate the propensity scores [10]. Thus, propensity scores were created through a binary logistic regression for the predicted probability of receiving a transplanted organ from a BCPD or non-BCPD as a function of donor age, donor gender, donor race, donor hypertension, donor diabetes, donor body mass index (BMI), recipient age, recipient gender, recipient Model for End-Stage Liver Disease (MELD) score, recipient hepatitis C virus (HCV) infection, recipient hepatocellular carcinoma (HCC), and cold ischemic time (see Table S1). We used the nearest neighbor matching with a caliper width set at 0.2 to identify BCPD and non-BCPD matched pairs [11]. We compared overall graft and patient survival in this propensity score-matched population to ensure results were similar to those obtained using the entire study population. All analyses were performed using the SPSS version 22 (IBM Corp., Armonk, NY, USA) with $P < 0.05$ as the level of statistical significance. This research was exempt of institutional review board (IRB) review as involved the analysis of an existing, de-identified publicly available database.

Results

A total of 28 961 patients received primary, single-organ deceased-donor liver transplantation in the USA between 2008 and 2013. There were 2316 (8.0%) recipients of BCPD. The baseline donor and recipient characteristics of the BCPD and non-BCPD cohorts are shown in Table 1. Donors with positive blood cultures were more likely to be older, female, black, diabetic, hypertensive and have a higher BMI compared to donors without positive blood cultures. Recipients of BCPD were more likely to be older compared to recipients of non-BCPD. There were no differences on initial maintenance immunosuppressive therapy between recipients of BCPD as compared to non-BCPD (Table S2).

Graft survival was significantly decreased in recipients of BCPD compared to recipients of non-BCPD ($P = 0.009$) as shown in Table 2. Patient survival was not significantly different between the BCPD and non-BCPD cohorts at 1 year ($P = 0.077$). Peri-operative mortality at 30 and 90 days was not different between

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Table 1. Baseline characteristics of the study population.

Variable	Non-BCPD (n = 26 645)	BCPD (n = 2316)	P value	Standardized difference
Recipient				
Age	54.8 ± 9.9	55.2 ± 9.8	0.050	−0.041
Male gender	17 941 (67.3)	1571 (67.8)	0.623	−0.011
Black race	2574 (9.7)	225 (9.7)	0.932	0.000
Hep C ± Hepatocellular cancer	2837 (10.7)	257 (11.1)	0.603	
Diabetes	5800 (21.8)	498 (21.5)	0.767	−0.007
Body mass index	28.6 ± 5.7	28.7 ± 5.8	0.779	−0.016
Creatinine, mg/dl	1.4 ± 1.1	1.4 ± 1.0	0.348	0.004
Prothrombin time INR	1.9 ± 1.2	1.9 ± 1.3	0.275	−0.001
Total bilirubin, mg/dl	8.6 ± 11.3	8.5 ± 11.1	0.801	0.011
MELD score	21.7 ± 10.7	21.7 ± 10.7	0.961	0.000
Length of hospital stay, days	15.1 ± 20.1	15.8 ± 25.7	0.575	−0.029
Donor				
Age	42 ± 16.8	43 ± 16.1	0.006	−0.063
Male gender	15 821 (59.4)	1325 (57.2)	0.042	0.045
Black race	4763 (17.9)	473 (20.4)	0.002	−0.064
Diabetes	3159 (11.9)	328 (14.2)	0.001	−0.068
Hypertension	9663 (36.3)	936 (40.4)	<0.001	0.084
Body mass index	27.4 ± 6.1	28.2 ± 6.9	<0.001	−0.101
Creatinine, mg/dl	1.6 ± 1.7	1.7 ± 1.8	0.003	−0.075
Transplantation				
Cold ischemic time, h	6.7 ± 3.07	6.6 ± 2.8	0.638	0.020

For categorical variables, number (%). For continuous variables, mean ± standard deviation Mann–Whitney U nonparametric test was used for comparing two group means.

Table 2. Kaplan–Meier analysis: comparison of survival rates by donor blood culture results.

	Entire population			Propensity-matched population		
Time point	Non-BCPD (95% CI)*	BCPD (95% CI)*	P value	Non-BCPD (95% CI)*	BCPD (95% CI)*	P value
Graft survival						
7-day	0.98 (0.978–0.982)	0.97 (0.963–0.977)	0.009	0.98 (0.974–0.986)	0.97 (0.963–0.977)	0.038
1-month	0.96 (0.958–0.962)	0.95 (0.941–0.959)		0.96 (0.952–0.968)	0.95 (0.941–0.959)	
6-month	0.91 (0.907–0.913)	0.90 (0.888–0.912)		0.92 (0.909–0.931)	0.90 (0.888–0.912)	
1-year	0.88 (0.876–0.884)	0.86† (0.846–0.874)		0.89 (0.877–0.903)	0.87† (0.856–0.884)	
Patient survival						
7-day	0.99 (0.989–0.991)	0.98 (0.974–0.986)	0.077	0.99 (0.985–0.995)	0.98 (0.974–0.986)	0.138
1-month	0.97 (0.968–0.972)	0.97 (0.963–0.977)		0.97 (0.964–0.976)	0.97 (0.963–0.977)	
6-month	0.93 (0.927–0.933)	0.93 (0.920–0.940)		0.94 (0.930–0.950)	0.93 (0.919–0.941)	
1-year	0.90 (0.896–0.904)	0.89 (0.877–0.903)		0.91 (0.898–0.922)	0.90 (0.887–0.913)	

*Survival estimates with 95% confidence intervals in parenthesis.

†Absolute risk difference at 1 year = 2%.

the cohorts either. Figures 1 and 2 show the graft and patient Kaplan–Meier survival curves.

There were 317 (13.7%) recipients of BCPD and 3221 (12.1%) recipients of non-BCPD who developed graft failure within the first year after transplantation. Information on the cause of graft failure was available in 227 BCPD and 2276 non-BCPD recipients. Among these patients, 34 (14.9%) recipients of BCPD and 282 (12.4%) recipients of non-BCPD developed graft failure primarily due to an infectious cause, but this difference was not statistically significant (P = 0.263). Similarly, rates of rejection as cause of graft failure were not statistically different between BCPD and non-BCPD groups (13.7% vs. 13.3%, P = 0.869).

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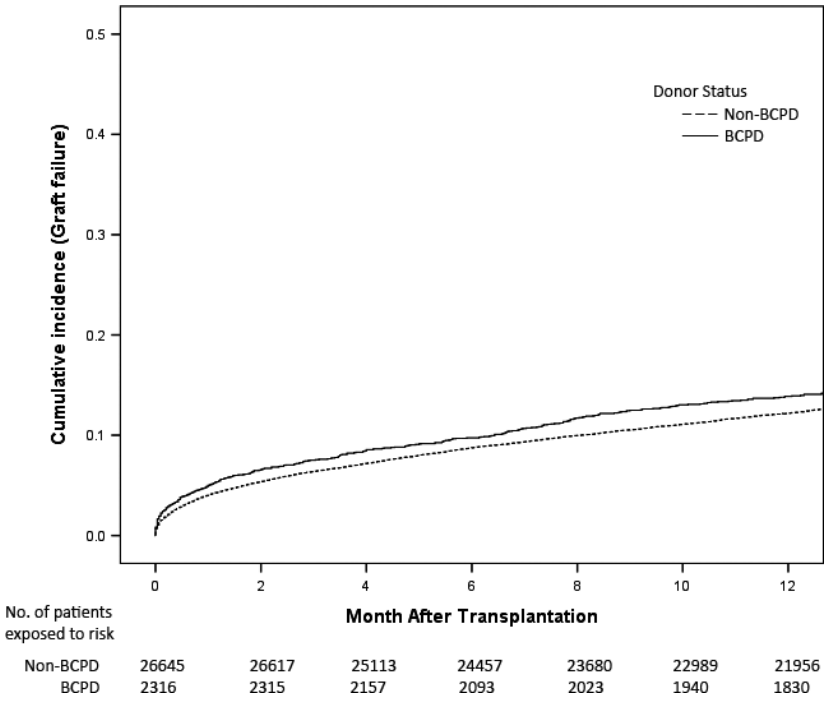

Figure 1 Graft survival curve by donor blood culture results.

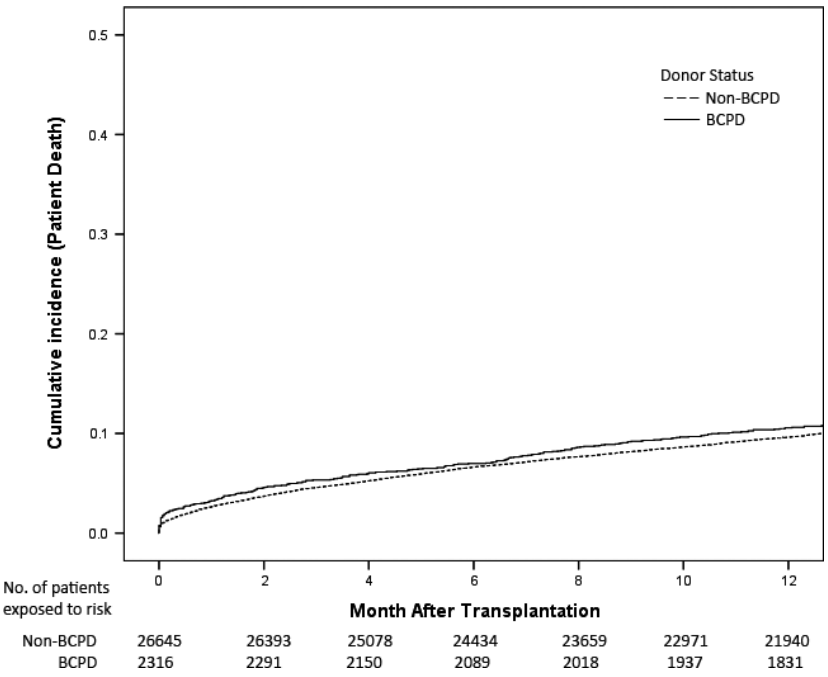

Figure 2 Patient survival curve by donor blood culture results.

We explored recipient and transplant procedure characteristics associated with graft failure among recipients of BCPD. We found that each increase in 1 point of the MELD score was independently associated with a higher risk of graft failure (adjusted HR, 1.02; 95% CI, 1.01–1.03). When the individual components of the MELD score were assessed, higher creatinine and higher bilirubin were independently associated with higher risk of graft failure.

In multivariable analysis, recipients of BCPD were more likely to experience graft failure compared to recipients of non-BCPD, after adjusting for donor age, donor gender, donor race, donor hypertension, donor diabetes, donor BMI, recipient age, recipient gender, recipient MELD score, recipient HCV, recipient HCC, and cold ischemic time (adjusted HR; 1.10, 95% CI 1.01–1.20; $P = 0.04$). In a similar multivariable analysis, BCPD was not associated with significant differences in

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patient death (adjusted HR; 1.06, 95% 0.96–1.18; $P = 0.222$). The complete results of the multivariable Cox regression models are shown in Table 3. Our analysis using propensity scores included 2279 patients in the BCPD cohort and 2279 patients in the non-BCPD cohort who were 1:1 matched based on similar donor age, donor gender, donor race, donor hypertension, donor diabetes, donor BMI, recipient age, recipient gender, recipient MELD score, recipient HCV infection, recipient HCC, and cold ischemic time. Table 4 shows the distribution of baseline donor and recipient characteristics of the propensity score-matched BCPD and non-BCPD cohorts demonstrating no significant differences. BCPD remained associated with an increased risk of graft failure ($P = 0.038$) whereas patient death was not significantly different between the BCPD and non-BCPD cohorts ($P = 0.138$). In a Cox regression model stratified by propensity score-matched pairs, BCPD was associated with graft failure (HR, 1.15; 95% CI, 1.02–1.31; $P = 0.03$).

Table 3. Results of Cox Model analysis for graft failure and patient mortality.

Variable	Graft failure aHR (95% CI)	Patient mortality aHR (95% CI)
Recipient		
Age, 10-year change	1.13 (1.01–1.2)	1.02 (1.01–1.03)
Male gender	1.01 (0.96–1.07)	0.99 (0.94–1.06)
Hep C	0.98 (0.86–1.14)	0.97 (0.83–1.14)
Hep C ± Hepatocellular cancer	0.83 (0.75–0.92)	0.78 (0.70–0.86)
MELD score, five unit change	1.06 (0.97–1.07)	1.02 (1.01–1.02)
Donor		
Age	1.09 (1.07–1.10)	1.08 (1.06–1.10)
Male gender	1.02 (0.97–1.07)	1.06 (1.01–1.13)
Black race	1.02 (0.96–1.09)	0.95 (0.89–1.03)
Diabetes	1.15 (1.07–1.24)	1.14 (1.04–1.24)
Hypertension	1.04 (0.98–1.11)	1.02 (0.96–1.1)
Body mass index, five unit change	0.99 (0.97–1.11)	1.01 (0.99–1.01)
Transplantation		
Cold ischemic time, h	1.03 (1.02–1.03)	1.02 (1.01–1.03)

Table 4. Baseline characteristics of the propensity score-matched populations.

Variable	Non-BCPD ($n = 2279$)	BCPD ($n = 2279$)	P value
Recipient			
Age	55.4 ± 9.9	55.3 ± 9.8	0.564
Male gender	1558 (68.4)	1547 (67.9)	0.727
Black race	225 (9.9%)	222 (9.7%)	0.881
Hep C ± Hepatocellular cancer	234 (10.3)	254 (11.2)	0.534
Diabetes	480 (21.1)	494 (21.7)	0.613
Body mass index	28.6 ± 5.7	28.7 ± 5.8	0.894
MELD score	21.6 ± 10.7	21.7 ± 10.7	0.727
Donor			
Age	43.1 ± 16.8	43 ± 16.1	0.813
Male gender	1305 (57.3)	1305 (57.3)	1.000
Black race	463 (20.3%)	470 (20.6%)	0.797
Diabetes	327 (14.3%)	323 (14.2%)	0.865
Hypertension	885 (38.8%)	921 (40.4%)	0.276
Body mass index	28.1 ± 6.6	28.2 ± 6.9	0.996
Creatinine, mg/dl	1.7 ± 2.0	1.7 ± 1.8	0.648
Transplantation			
Cold ischemic time, h	6.6 ± 2.8	6.6 ± 2.8	0.923

For categorical variables, number (%). For continuous variables, mean ± standard deviation Mann–Whitney *U* nonparametric test was used for comparing two group means.

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Discussion

In this large, contemporary analysis of liver transplant recipients, we found that the use of donors who had a clinical infection confirmed with positive blood cultures prior to organ procurement was associated with decreased graft survival. We did not find a negative effect of BCPD in recipient survival.

Freeman *et al.* [3] estimated that 5% of donors were bacteremic at time of organ procurement in a retrospective analysis of 1775 donors cared for by the New England Organ Bank in the USA between 1990 and 1998. Lumbreras *et al.* [4] found a similar rate of donor bacteremia in 569 liver and heart donors in Madrid, Spain, between 1990 and 1998. Cerutti *et al.* [12] reported a rate of bacteremia of 21% among 610 liver donors in Turin, Italy, between 1998 and 2002. The latter study included symptomatic bacteremia that could have occurred days prior to organ procurement, in addition to bacteremia at time of recovery of organs which could explain the large differences in rates compared to the other two studies. Furthermore, the mean age of donors in the Freeman *et al.* and Lumbreras *et al.* studies was in the 1930s, compared to mid-1950s in the Cerutti *et al.* study. Our analysis included data from solid-organ donors between 2008 and 2013 across the USA, and found a rate of 8% for clinical infection with confirmed positive blood cultures prior to organ procurement. Discrepancies in time of blood cultures collection (days prior to organ procurement versus at time of organ procurement) and reason for blood culture collection (presence of clinical infection versus routine surveillance) may explain the differences in BCPD rates between our study and the others. The UNOS BCPD definition may not include results of routine surveillance blood cultures obtained at time of organ procurement; therefore, our overall rate of BCPD likely underestimates the true prevalence of positive blood cultures in current donors. Furthermore, by the time brain death occurs in donors, several immunologic disturbances that predispose to infection and bacteremia have been described [13,14]. Clinical manifestations of infection can be subtle and more than 60% of donors may not develop fever even in the presence of positive blood cultures at time of organ procurement [4]. Therefore, the UNOS BCPD definition used for our study may miss asymptomatic and subclinical bacteremia episodes after brain death.

Cerutti *et al.* [12] reported one-year graft survival rates of 81% for recipients of BCPD versus 83% for recipients of non-BCPD. This difference was not found to be statistically significant. In our study, we were able to demonstrate a significant difference in graft survival in recipients of BCPD versus non-BCPD. Our results expand the understanding of BCPD in liver transplant outcomes by overcoming statistical power limitations of prior smaller studies. We found differences in graft survival on bivariate and multivariable analyses including propensity score matching, but these differences did not translate in a significant decrease in patient survival. Putting our findings in a clinical context, we observed an average of one excess case of graft failure per 50 liver transplants using BCPD compared to non-BCPD. Thus, in a medical center where 100 liver transplants are performed annually with a BCPD incidence rate of ~8% as indicated by our study, it would take up to 6.25 years to have one excess case of graft failure attributed to BCPD. In the current context of organ shortage and lifesaving nature of liver transplantation, the use of donors with positive blood cultures should be considered acceptable. Future studies are needed to identify which subgroups of BCPD are at the highest risk of graft failure and characterize the underlying mechanisms.

We found that BCPD were more likely to be older, black, female and have more comorbidities such as diabetes, hypertension, and higher BMIs compared to non-BCPD. This is consistent with other studies of donors with positive blood cultures [12], and may be related to increased risk of bacteremia and other complications as age and comorbidities increase. It is possible that these baseline characteristics could have accounted for some of the differences in graft failure rates observed between recipients of BCPD versus non-BCPD. However, we conducted adjusted and propensity score-matched analyses showing that the increased risk of graft failure in BCPD was independent of sociodemographic and comorbid conditions. Furthermore, there were no statistically significant differences in baseline characteristics among recipients of BCPD and non-BCPD who developed graft failure (Tables S3 and S4). Therefore, our findings indicate that the excess graft failure associated with BCPD was not fully explained by differences in baseline characteristics.

There are alternative potential explanations to the decreased graft survival observed in recipients of BCPD. Donors may develop liver injury in the setting of sepsis and bacteremia prior to organ procurement, and this could lead to liver dysfunction that could persist and/or progress in the recipient [15], even if infection clears up by the time of transplantation. Supporting this hypothesis, studies have shown that 3–15% of sepsis survivors

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who received routine medical care and had evidence of hepatobiliary dysfunction on presentation progressed to develop some degree of persistent hepatobiliary dysfunction by 28 days [16–18]. Studies have shown that post-transplant bacteremia in recipients of liver allografts carries significant morbidity and mortality [19,20]; therefore, bacteremia in the donor could have a negative effect on the outcomes of liver recipients. It is also possible that decreased graft survival could be related to clinical and subclinical donor-to-recipient infection transmission. We were unable to assess infection transmission with the data available in UNOS. Notably, prior studies of BCPD showed that donor-to-recipient transmission is rare [3–6,12], and we found no correlation between BCPD and infection as the main cause of graft failure. Nevertheless, recent reports suggest that liver transplant recipients are at higher risk of infection transmission compared to other solid-organ recipients despite appropriate antibiotic prophylaxis [21,22]. Doucette *et al.* [21] hypothesized that the increased infection risk in liver allografts could be related to the larger tissue and vascular volume, phagocytic Kupffer cells that can play host to microorganisms, and disadvantageous liver recipient characteristics including severe illness as suggested by high MELD scores at time of transplantation, frequent leukopenia, immunosuppression, and limited antibiotic penetration to the transplanted liver. Additionally, longer antibiotic courses used in liver donors and recipients in the setting of BCPD may pose a risk for allograft injury [23].

Our study had limitations that should be mentioned. Overall, these limitations are similar to the ones described in prior UNOS dataset analyses [8,9]. The UNOS database does not collect information on the specific organism isolated from blood cultures. This imposed a significant restriction to study specific pathogens associated with the highest risk of graft dysfunction and to evaluate the possibility of donor-to-recipient infection transmission and its consequences. A proportion of positive blood cultures may have been due to microorganisms often considered contaminants or non-pathogenic. However, the UNOS definition of BCPD only included cases with a clinical infection syndrome of blood source that were further confirmed by blood cultures therefore true donor infections are most likely. The UNOS database does not provide information on the time elapsed from positive blood culture to date of transplantation, antibiotic usage, or infection severity. Transplant teams carefully selected which allografts were used for transplantation based on guidelines and routine practice; therefore, selection bias is inevitable. Organs available from donors with unresolved sepsis and those who were infected with multidrug-resistant organisms were most likely excluded.

In conclusion, BCPD was associated with decreased graft survival in deceased-donor liver transplant recipients. However, these differences in graft survival did not impact patient survival in this large cohort. As liver transplantation is often a lifesaving operation and there is a large gap between supply and demand for livers, decreased BCPD graft survival without a significant effect on patient survival would be considered acceptable. Careful consideration of BCPD and further investigation on the mechanisms of decreased graft survival in BCPD are warranted.

Authorship

MAH and RG: conceived and designed the study, and were involved in all the stages of the study. MX: contributed to data management, data analysis, interpretation of results, and to writing the manuscript. VV, MBS, MFD and JB: contributed to interpretation of results and to writing the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

None of the authors have any competing interests in the manuscript.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Distribution of propensity scores.

Table S1. Propensity score logistic regression model for blood culture positive donor (BCPD).

Table S2. Initial maintenance immunosuppressive therapy in liver transplant recipients by donor blood culture results.

Table S3. Baseline characteristics of liver transplant recipients of BCPD versus non BCPD who developed graft failure (includes patients with complete data available).

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Table S4. Baseline characteristics table for recipients of BCPD versus non BCPD with graft failure after propensity score (includes patients with complete data available).

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