OPEN

Liver Transplantation for Budd-Chiari Syndrome in the MELD Era

Saleh A. Alqahtani, MD,[1,2,3] Carolin Schneider, MD,[4] Omar T. Sims, PhD,[5] Ahmet Gurakar, MD,[2] Hani Tamim, PhD,[6] Alan Bonder, MD,[7] and Behnam Saberi, MD[7]

Background. To evaluate clinical characteristics and factors associated with survival among liver transplantation (LT) recipients with Budd-Chiari syndrome (BCS), with or without transjugular intrahepatic portosystemic shunt (TIPS), in the post–Model for End-stage Liver Disease era. **Methods.** We extracted data from the United Network for Organ Sharing database on all adult (≥18 y old) waitlisted candidates and recipients of LT with BCS in the United States between 2002 and 2019. Multivariable Cox regression was used to determine predictors of mortality and hazard ratios (HRs). **Results.** A total of 647 BCS patients were waitlisted between 2002 and 2019. BCS was an indication for LT in 378 (0.2%) of all adult LT recipients during the study period. Of BCS patients who received LT, approximately three-fourths (72.3%) were alive for up to 10 y. We found no significant difference in LT outcomes in BCS patients with or without TIPS. Longer length of hospital stay following LT (HR, 1.32; 95% confidence interval [CI], 1.19-1.47), Black/African American race (HR, 2.24; 95% CI, 1.38-3.64), diabetes (HR, 3.17; 95% CI, 1.62-6.21), donor risk index (HR, 1.44; 95% CI, 1.05-1.99), and lower albumin levels at the time of transplantation (HR, 0.66; 95% CI, 0.50-0.88) were negatively associated with survival after LT. Interestingly, neither the Model for End-stage Liver Disease nor prior TIPS showed a significant association with survival after LT. **Conclusions.** These findings demonstrate good comparable survival among TIPS versus no TIPS in LT recipients with BCS. The decision for TIPS versus LT should be individualized on a case-by-case basis.

(*Transplantation Direct* 2022;8: e1407; doi: 10.1097/TXD.0000000000001407).

INTRODUCTION

Budd-Chiari syndrome (BCS) is a rare condition caused by hepatic venous outflow tract obstruction.[1] BCS has a heterogeneous clinical presentation, ranging from asymptomatic cases to fulminant liver failure.[2] If left untreated, symptomatic BCS has a high mortality rate.[3] Before specific therapy became available, 90% of patients died within 3 y, mostly of ascites, gastrointestinal bleeding, and liver failure.[4,5] Innovations in interventional radiology and a better understanding of underlying diseases have dramatically improved therapeutic strategies.[6] Besides hepatic vein recanalization and stenting, transjugular intrahepatic portosystemic shunt (TIPS) is an option for severe acute or subacute BCS.[7] However, TIPS has to be considered on a case-by-case basis and may not be feasible in all BCS patients because of the degree of liver failure, the extent of thrombosis, and concerns for shunt occlusion.[8]

Liver transplantation (LT) may be the only option for patients with BCS who have decompensated cirrhosis or acute liver failure, those who are not candidates for other therapies, and for whom other treatments are ineffective.[9,10] Another indication for LT in BCS is the presence of hepatocellular carcinoma (HCC) within the Milan criteria.[11] Advances in LT technology and adoption of the Model for End-stage Liver Disease (MELD) score for deceased donor liver allocation may have led to improved survival in BCS following LT.[12]

Received 29 June 2022. Revision received 9 September 2022.

Accepted 26 September 2022.

[1] Center for Outcomes Research in Liver Diseases, Washington, DC.

[2] Division of Gastroenterology and Hepatology, Johns Hopkins University, Baltimore, MD.

[3] Liver Transplant Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.

[4] The Institute for Translational Medicine and Therapeutics, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

[5] School of Medicine, School of Public Health, School of Arts and Sciences, University of Alabama at Birmingham, Birmingham, AL.

[6] College of Medicine, Alfaisal University, Riyadh, Saudi Arabia.

[7] Division of Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

The authors declare no funding or conflicts of interest.

S.A.A. and B.S. conceived the research idea. B.S. and A.B. were involved in study design. S.A.A. and B.S. obtained the datasets. H.T. and B.S. performed the statistical analysis. B.S. and H.T. reviewed and interpreted the results. C.S., O.S., A.G., and B.S. drafted the article. All authors reviewed, provided substantial inputs, and approved the final version of the article.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Saleh A. Alqahtani, MD, Division of Gastroenterology & Hepatology, Johns Hopkins University, 600 North Wolfe Street, Blalock Suite 4, Baltimore, MD 21287. (salqaht1@jhmi.edu).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001407

TABLE 1.

Comparison of BCS liver transplant candidates, based on their liver transplant status between 2002 and 2019

Characteristics	Total, N = 647 (100.0)	Received liver transplant		P
		Yes, N = 378 (58.4)	No, N = 269 (41.5)	
Age, mean (SD)	40.8 (12.9)	40.9 (12.8)	40.7 (13.1)	0.87
Gender, n (%)				
Male	267 (41.3)	157 (41.5)	110 (40.9)	0.87
Female	380 (58.7)	221 (58.5)	159 (59.1)	
Race, n (%)				
White	474 (73.3)	275 (72.8)	199 (74.0)	0.41
Black/AA	85 (13.1)	55 (14.6)	30 (11.2)	
Hispanic	58 (9.0)	29 (7.7)	29 (10.8)	
Asian	24 (3.7)	16 (4.2)	8 (3.0)	
Other	6 (0.9)	3 (0.8)	3 (1.1)	
ABO, n (%)				
A	265 (41.0)	151 (39.9)	114 (42.4)	0.18
B	95 (14.7)	55 (14.6)	40 (14.9)	
AB	31 (4.8)	24 (6.3)	7 (2.6)	
O	256 (39.6)	148 (39.2)	108 (40.1)	
BMI (kg/m^2), mean (SD)	27.0 (5.5)	27.0 (5.6)	27.1 (5.4)	0.86
Diabetes, n (%)	35 (5.4)	20 (5.3)	15 (5.6)	0.87
HCC, n (%)	58 (9.0)	40 (10.6)	18 (6.7)	0.09
HE, n (%)	346 (53.5)	242 (64.0)	104 (38.7)	**<0.001**
Ascites, n (%)	458 (70.8)	314 (83.1)	144 (53.5)	**<0.001**
SBP, n (%)	45 (7.0)	27 (7.1)	18 (6.7)	0.82
PVT, n (%)	180 (27.8)	129 (34.1)	51 (19.0)	**<0.001**
Dialysis, n (%)	93 (14.4)	64 (16.9)	29 (10.8)	**0.03**
TIPS, n (%)	215 (33.2)	121 (32.0)	94 (34.9)	0.43
Life support, n (%)	40 (6.2)	25 (6.6)	15 (5.6)	0.59
Status 1, n (%)	48 (12.7)	48 (12.7)	NA	NC
MELD score, mean (SD)	22 (9)	24 (9)	19 (9)	**<0.001**
MELD exception, mean (SD)	24 (10)	28 (8)	18 (10)	**<0.001**
Sodium (mEq/L), mean (SD)	136.5 (5.4)	135.0 (5.7)	138.4 (4.4)	**<0.001**
Creatinine (mg/dL), mean (SD)	1.6 (1.5)	1.7 (1.7)	1.3 (1.3)	**<0.001**
Bilirubin (mg/dL), mean (SD)	6.0 (9.0)	7.2 (10.0)	4.4 (7.0)	**<0.001**
INR, mean (SD)	2.3 (1.6)	2.4 (1.7)	2.1 (1.6)	**0.04**
Albumin (g/dL), mean (SD)	3.4 (0.8)	3.3 (0.8)	3.5 (0.8)	**<0.001**
Wait time (d), mean (SD)	321.6 (676.5)	321.6 (676.5)	NA	NC
LOS	20.8 (27.4)	20.8 (27.4)	NA	NC
UNOS/OPTN region, n (%)				
1	35 (5.4)	15 (4.0)	20 (7.4)	**<0.001**
2	78 (12.1)	44 (11.6)	34 (12.6)	
3	94 (14.5)	72 (19.0)	22 (8.2)	
4	55 (8.5)	25 (6.6)	30 (11.2)	
5	98 (15.1)	49 (13.0)	49 (18.2)	
6	12 (1.9)	8 (2.1)	4 (1.5)	
7	58 (9.0)	28 (7.4)	30 (11.2)	
8	68 (10.5)	38 (10.1)	30 (11.2)	
9	33 (5.1)	19 (5.0)	14 (5.2)	
10	48 (7.4)	28 (7.4)	20 (7.4)	
11	68 (10.5)	52 (13.8)	16 (5.9)	
Donor characteristics				
Age (y), mean (SD)	38.0 (16.2)	38.0 (16.2)		NC
Gender				
Male	221 (58.5)	221 (58.5)		NC
Female	157 (41.5)	157 (41.5)		
BMI (kg/m^2), mean (SD)	26.4 (5.6)	26.4 (5.6)		NC
Race, n (%)				

Continued next page

TABLE 1.(Continued)

Comparison of BCS liver transplant candidates, based on their liver transplant status between 2002 and 2019

Characteristics	Total, N = 647 (100.0)	Received liver transplant		P
		Yes, N = 378 (58.4)	No, N = 269 (41.5)	
White	252 (66.7)	252 (66.7)		NC
Black/AA	61 (16.1)	61 (16.1)		
Hispanic	51 (13.5)	51 (13.5)		
Asian	8 (2.1)	8 (2.1)		
Other	6 (1.6)	6 (1.6)		
ABO, n (%)				
A	144 (38.1)	144 (38.1)		NC
B	47 (12.4)	47 (12.4)		
AB	13 (3.4)	13 (3.4)		
O	174 (46.0)	174 (46.0)		
Total cold ischemic time (h), mean (SD)	6.9 (2.5)	6.9 (2.5)	–	NC
DRI, mean (SD)	1.5 (0.6)	1.5 (0.6)	–	NC

Bold indicates significance at 0.05.

AA, African American; BCS, Budd-Chiari syndrome; BMI, body mass index; DRI, donor risk index; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; INR, international normalized ratio; LOS, length of hospital stay; MELD, Model for End-stage Liver Disease; NA, not available; NC, not calculated; OPTN, Organ Procurement and Transplantation Network; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt; UNOS, United Network for Organ Sharing.

Prior studies suggest that survival following LT in BCS patients may depend on the severity of BCS at the time of LT.[13–15] Former studies reported survival rates of LT in BCS patients ranging from 5-y survival of only 35% to 50% to 10-y survival of >80%.[9,16,17] Still, there are limited recent data on the characteristics, outcomes, and predictors of survival in BCS patients undergoing LT, particularly in the post-MELD era. Therefore, we aimed to study the rate of LT in BCS patients and the factors associated with their survival in the post-MELD era. In addition, we focus on the role of TIPS in this context.

MATERIALS AND METHODS

Study Design

For this retrospective cohort study, we extracted data from the United Network for Organ Sharing (UNOS) database on all adult (≥18 y old) waitlisted candidates and LT recipients with BCS in the United States between 2002 and 2019 to limit our analysis to the post-MELD era.

Outcomes of interest were survival estimates among patients with BCS based on pretransplant TIPS status and to evaluate the predictors of mortality among BCS LT recipients. The data reported here have been supplied by the UNOS as the contractor for the Organ Procurement and Transplantation Network (OPTN). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the US Government. Because this was a retrospective review of dataset available in a national database, an ethics committee review is not applicable.

Variables

Clinical characteristics included but were not limited to age, gender, race, body mass index, MELD score, other comorbid medical conditions, laboratory, previous TIPS procedure, and LT status.

Statistical Analysis

Measures of central tendency and frequency distributions were used to characterize the sample. The independent samples *t* test and chi-square test were used to compare patient groups on continuous and categorical variables, respectively. Multivariable Cox proportional hazard regression with follow-up as the underlying time variable was used to determine predictors of mortality. Variables associated with both the exposure of interest and causally associated with the outcome were included in regression models as possible confounders. Assessment of interaction terms between each exposure of interest and the underlying time variable did not suggest significant deviation from proportional hazards. Results were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Survival analysis was carried out using the Kaplan-Meier curve. Differences were considered statistically significant when $P < 0.05$.

RESULTS

LT in BCS Patients in the Post-MELD Era

Among all waitlisted patients for LT between 2002 and 2019, 647 (0.2%) had BCS (Table 1). BCS was an indication for LT in 378 (0.2%) recipients during the study period (Table 2). Their mean follow-up was 5.1 y (SD = 4.8 y). The majority were female (58.7%), White (73.3%), and with a mean age of 40.8 y (SD = 12.9 y) (Table 1).

First, we evaluated the characteristics of BCS patients who underwent LT. Among adult waitlisted candidates with BCS, 58.4% underwent LT (Table 1). A higher proportion of patients who received LT had portal vein thrombosis (34.1% versus 19.0%; $P < 0.001$), ascites (83.1% versus 53.5%; $P < 0.001$), and hepatic encephalopathy (HE) (64.0% versus 38.7%; $P < 0.001$) and were on dialysis (16.9% versus 10.8%; $P = 0.03$) (Table 1) compared with non-LT recipients with BCS. Interestingly, the frequency of TIPS was not different between the BCS patients who received and did not receive LT (32.0% versus 34.9%; $P = 0.43$) (Table 1). Those who received LT had a higher MELD score (24 [SD = 9] versus 19 [SD = 9]; $P < 0.001$), creatinine (1.7 [SD = 1.7] versus 1.3 [SD = 1.3]; $P < 0.001$), and bilirubin (7.2 [SD = 10.0] versus 4.4 [SD = 7.0]; $P < 0.001$), whereas those who did not receive LT had higher albumin (3.5 [SD = 0.8] versus 3.3 [SD

TABLE 2.

Comparison of BCS liver transplant recipients based on survival status after liver transplant

Characteristics	Survival, N = 288 (76.2)	Death, N = 90 (23.8)	*P*
Recipient characteristics			
Age (y), mean (SD)	40.3 (12.5)	42.6 (13.6)	0.14
Gender, n (%)			
Male	125 (43.4)	32 (35.6)	0.19
Female	163 (56.6)	58 (64.4)	
Race, n (%)			**0.01**
White	218 (75.7)	57 (63.3)	
Black/AA	32 (11.1)	23 (25.6)	
Hispanic	22 (7.6)	7 (7.8)	
Asian	13 (4.5)	3 (3.3)	
Other	3 (1.0)	0 (0.0)	
ABO, n (%)			0.72
A	112 (38.9)	39 (43.3)	
B	45 (15.6)	10 (11.1)	
AB	18 (6.3)	6 (6.8)	
O	113 (39.2)	35 (38.9)	
BMI (kg/m^2), mean (SD)	26.9 (5.5	27.3 (5.9	0.50
Diabetes, n (%)	9.5 (3.5)	10.4 (11.1)	**0.01**
HCC, n (%)	30 (10.4)	10 (11.1)	0.85
HE, n (%)	181 (62.8)	61 (67.8)	0.39
Ascites, n (%)	235 (81.6)	79 (87.8)	0.17
SBP, n (%)	19 (6.6)	8 (8.9)	0.46
PVT, n (%)	101 (35.1)	28 (31.1)	0.49
Dialysis, n (%)	49 (17.0)	15 (16.7)	0.94
TIPS, n (%)	94 (32.6)	27 (30.0)	0.64
Life support, n (%)	19 (6.6)	6 (6.7)	0.98
Status 1, n (%)	37 (12.8)	11 (12.2)	0.88
MELD score, mean (SD)	24.2 (9.2)	25.1 (9.3)	0.42
MELD exception, mean (SD)	28 (8)	28 (8)	0.72
Sodium (mEq/L), mean (SD)	135.4 (5.4)	134.9 (4.9)	0.38
Creatinine (mg/dL), mean (SD)	1.8 (1.7)	1.6 (1.7)	0.52
Bilirubin (mg/dL), mean (SD)	6.7 (9.6)	8.9 (11.2)	0.07
INR, mean (SD)	2.4 (1.6)	2.5 (1.8)	0.55
Albumin (g/dL), mean (SD)	3.4 (0.7)	3.0 (0.7)	**<0.001**
Wait time (d), mean (SD)	314.3 (651.1)	344.8 (755.5)	0.71
LOS (d), mean (SD)	17.4 (16.5)	31.8 (45.8)	**0.004**
UNOS/OPTN region, n (%)			
1	11 (3.8)	4 (4.4)	0.21
2	31 (10.8)	13 (14.4)	
3	57 (19.8)	15 (16.7)	
4	19 (6.6)	6 (6.7)	
5	42 (14.6)	7 (7.8)	
6	3 (1.0)	5 (5.6)	
7	22 (7.6)	6 (6.7)	
8	32 (11.1)	6 (6.7)	
9	14 (4.9)	5 (5.6)	
10	21 (7.3)	7 (7.8)	
11	36 (12.5)	16 (27.8)	
Donor characteristics			
Age (y), mean (SD)	38.0 (15.7)	38.1 (18.1)	0.94
Gender, n (%)			
Male	163 (56.6)	58 (64.4)	0.19
Female	125 (43.4)	32 (35.6)	
BMI (kg/m^2), mean (SD)	26.5 (5.8)	26.1 (4.7)	0.50
Race, n (%)			
White	196 (68.1)	56 (62.2)	0.75
Black	45 (15.6)	16 (17.8)	
Hispanic	37 (12.9)	14 (15.6)	
Asian	5 (1.7)	3 (3.3)	
Other	5 (1.7)	1 (1.1)	
Total cold ischemic time (h), mean (SD)	6.8 (2.4)	7.4 (2.7)	0.05
DRI, mean (SD)	1.45 (0.58)	1.58 (0.67)	0.08

Bold indicate significance at 0.05.

AA, African American; BCS, Budd-Chiari syndrome; BMI, body mass index; DRI, donor risk index; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; INR, international normalized ratio; LOS, length of hospital stay; MELD, Model for End-stage Liver Disease; OPTN, Organ Procurement and Transplantation Network; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt; UNOS, United Network for Organ Sharing.

= 0.8]; $P < 0.001$) and sodium (138.4 [SD = 4.4] versus 135.0 [SD = 5.7]; $P < 0.001$; Table 1).

TIPS in BCS

Next, we evaluated the clinical characteristics of LT recipients with or without pretransplant TIPS. Nearly a third (32.0%) of BCS patients who received LT had TIPS before transplant (Table 3). LT recipients with TIPS had a longer wait time on the list than patients without TIPS (532 versus 222 d; $P < 0.001$), had lower MELD scores (23 versus 25; $P = 0.02$), and had a lower rate of status 1 (7.4% versus 15.2%; $P = 0.03$) (Table 3). We also evaluated the characteristics of nontransplant recipients based on the pretransplant TIPS status. The characteristics of listed patients with BCS who did not undergo LT based on TIPS status are outlined in Table S1 (SDC, http://links.lww.com/TXD/A474).

LT Recipients With BCS and Status 1

Next, we evaluated the clinical characteristics of BCS LT recipients with status 1 (Table S2, SDC, http://links.lww.com/TXD/A474). A total of 48 (12.7%) BCS patients were transplanted as status 1. Patients in status 1 had significantly shorter wait times before transplant (12.5 versus 366.5 d; $P < 0.001$). They had a higher serum creatinine, bilirubin, and international normalized ratio at the time of transplantation (all $P < 0.001$). There was a higher rate of HE, dialysis, and life support in status 1 patients. Patients who were transplanted as status 1 were less likely to have undergone TIPS (18.7 versus 33.9%; $P = 0.04$). None of the BCS patients transplanted as status 1 had a diagnosis of HCC (0% versus 12.1%; $P = 0.01$; Table S2, SDC, http://links.lww.com/TXD/A474).

LT Recipients With BCS and HCC

Additionally, we evaluated the characteristics of BCS patients with HCC who received LT, as HCC is a major determinant of posttransplant outcomes (Table S3, SDC, http://links.lww.com/TXD/A474). Of the 40 HCC and BCS cases, 62.5% were female, and 67.5% were White (Table S3, SDC, http://links.lww.com/TXD/A474). HCC as a cause of transplant was not associated with decreased survival after transplant (Table 2). Interestingly, 88% of BCS patients with HCC and available alpha-fetoprotein data showed low levels of alpha-fetoprotein

TABLE 3.

Comparison of liver transplant recipients with BCS based on the pretransplant TIPS status between 2002 and 2019

Characteristics	TIPS		P
	No, N = 257	Yes, N = 121	
Age (y), mean (SD)	41.3 (12.3)	40.6 (13.0)	0.63
Gender, n (%)			
Male	110 (42.8)	47 (38.8)	0.47
Female	147 (57.2)	74 (61.2)	
Race, n (%)			
White	184 (71.6)	91 (75.2)	0.34
Black/AA	42 (16.3)	13 (10.7)	
Hispanic	21 (8.2)	8 (6.6)	
Asian	8 (3.1)	8 (6.6)	
Other	2 (0.8)	1 (0.8)	
BMI (kg/m^2), mean (SD)	27.1 (5.8)	26.7 (5.2)	0.48
Diabetes, n (%)	14 (5.4)	6 (5.0)	0.84
HCC, n (%)	22 (8.6)	18 (14.9)	0.06
HE, n (%)	167 (65.0)	75 (62.0)	0.57
Ascites, n (%)	216 (84.0)	98 (81.0)	0.46
SBP, n (%)	20 (7.8)	7 (5.8)	0.48
PVT, n (%)	82 (31.9)	47 (38.8)	0.19
Dialysis, n (%)	47 (18.3)	17 (14.0)	0.30
Life support, n (%)	20 (7.8)	5 (4.1)	0.18
Status 1, n (%)	39 (15.2)	9 (7.4)	**0.03**
MELD score, mean (SD)	25 (9)	23 (9)	**0.02**
MELD exception, mean (SD)	29 (8)	27 (7)	**0.07**
Sodium (mEq/L), mean (SD)	135.2 (5.1)	135.6 (5.4)	0.50
Creatinine (mg/dL), mean (SD)	1.8 (1.7)	1.6 (1.7)	0.34
Bilirubin (mg/dL), mean (SD)	7.8 (10.1)	5.9 (9.7)	0.10
INR, mean (SD)	2.5 (1.9)	2.3 (1.1)	0.41
Albumin (g/dL), mean (SD)	3.2 (0.7)	3.4 (0.8)	0.07
Wait time (d), mean (SD)	222.4 (471.2)	532.1 (947.8)	**<0.001**
LOS (d)	21.8 (29.5)	18.8 (22.3)	0.34
UNOS/OPTN region, n (%)			
1	11 (4.3)	4 (3.3)	0.09
2	28 (10.9)	16 (13.2)	
3	61 (23.7)	11 (9.1)	
4	15 (5.8)	10 (8.3)	
5	32 (12.5)	17 (14.0)	
6	6 (2.3)	2 (1.7)	
7	15 (5.8)	13 (10.7)	
8	21 (8.2)	17 (14.0)	
9	13 (5.1)	6 (5.0)	
10	19 (5.1)	9 (7.4)	
11	36 (14.0)	16 (13.2)	
Donor characteristics			
Age (y), mean (SD)	38.0 (16.4)	38.1 (16.0)	0.96
Gender			
Male	150 (58.4)	71 (58.7)	0.95
Female	107 (41.6)	50 (41.3)	
BMI (kg/m^2), mean (SD)	26.3 (5.5)	26.7 (5.8)	0.44
Race, n (%)			
White	168 (65.4)	84 (69.4)	0.50
Black/AA	41 (16.0)	20 (16.5)	
Hispanic	36 (14.0)	15 (12.4)	
Asian	6 (2.3)	2 (1.7)	
Other	6 (2.3)	0 (0.0)	
ABO, n (%)			
A	97 (37.7)	47 (38.8)	0.94
B	33 (12.8)	14 (11.6)	
AB	8 (3.1)	5 (4.1)	
O	119 (46.3)	55 (45.5)	
Total cold ischemic time (h), mean (SD)	7.1 (2.4)	6.7 (2.7)	0.20
DRI, mean (SD)	1.5 (0.6)	1.5 (0.6)	0.74

Bold indicate significance at 0.05.

AA, African American; BCS, Budd-Chiari syndrome; BMI, body mass index; DRI, donor risk index; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; INR, international normalized ratio; LOS, length of hospital stay; MELD, Model for End-stage Liver Disease; OPTN, Organ Procurement and Transplantation Network; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt; UNOS, United Network for Organ Sharing.

(<20 ng/mL). A majority of these patients (72.4%) had only 1 HCC lesion, and in 87.5%, the HCC lesion was in the right lobe (Table S4, SDC, http://links.lww.com/TXD/A474). The mean tumor size was 2.3 cm (SD = 1.1 cm) (Table S4, SDC, http://links.lww.com/TXD/A474). BCS patients transplanted for HCC showed a lower rate of HE (55.0% versus 86.4%; $P < 0.001$), lower MELD score (17.5 versus 25.2; $P < 0.001$), and longer wait time (732.7 versus 272.9 d; $P = 0.02$) compared with non-HCC LT recipients with BCS (Table S3, SDC, http://links.lww.com/TXD/A474). Overall, 59% of patients with HCC received 1 or more locoregional therapies (Table S4, SDC, http://links.lww.com/TXD/A474).

Explant data were available for 17 patients with HCC. Overall, 8 (47%) patients had no viable lesion on the explant. One patient (5%) had a microvascular invasion. As for tumor differentiation, 35.3% had well-differentiated HCC, 17.7% had moderately differentiated HCC, and 47% had complete necrosis of the HCC lesion. Three (17.8%) patients had multifocal HCC on the explant. None of the explant livers showed satellite lesions or lymph node involvement (Table S4, SDC, http://links.lww.com/TXD/A474).

Survival After LT in BCS Patients

Among BCS patients who received LT, 72.3% were alive for up to 10 y (Figure 1). Those who survived had higher albumin at removal (3.4 [SD = 0.7] versus 3.0 [SD = 0.7]; $P < 0.001$) , whereas those who died had a higher percentage of diabetes (11.1% versus 3.5%; $P = 0.01$) and a higher number of post-treatment hospitalization days (31.8 [SD = 45.8] versus 17.4 [SD = 16.5]; $P = 0.004$; Table 2). Post-LT survival in BCS at 5 and 10 y was 81.3% and 70.8% in the TIPS group compared with the no-TIPS group at 80.6% and 72.7% ($P = 0.93$). We performed multivariate Cox proportional hazard modeling to identify predictors of mortality among transplanted BCS patients (Table 4). Factors that increased mortality were longer length of hospital stay following LT (HR, 1.32; 95% CI, 1.19-1.47), Black/African American (AA) race (HR, 2.24; 95% CI, 1.38-3.64), donor risk index (DRI) (HR, 1.44; 95% CI, 1.05-1.99), and diabetes (HR, 3.17; 95% CI, 1.62-6.21). Albumin was negatively associated (HR, 0.66; 95% CI, 0.50-0.88) with mortality after LT (Table 4). Interestingly, neither TIPS nor MELD score had a significant effect on survival after LT (Table 4). Figure S1 (SDC,

http://links.lww.com/TXD/A474) shows waitlist mortality stratified by TIPS among nontransplanted patients. The subgroup that had TIPS had a trend toward a better outcome than those with no TIPS (P = 0.09). However, the statistical insignificance might be due to the low power in this subgroup because of the small sample size.

DISCUSSION

In the current study, we show a favorable 10-y post-LT survival of 72.3% among BCS patients in the post-MELD era. Factors associated with mortality in transplanted patients with BCS were diabetes, Black/AA race, DRI, and length of hospital stay following LT. In contrast, higher albumin at the time of transplantation was associated with a reduced risk of mortality after LT. In prior studies, factors associated with a worse prognosis in BCS patients receiving treatment included older age at diagnosis, chronic disease at presentation, more severe liver failure, and refractory ascites.[18–20]

Innovations in interventional techniques and the increasing knowledge of the pathophysiology of BCS have changed therapeutic algorithms for BCS in the recent decades.[21] The severity of BCS may depend on the extent and chronicity of hepatic vein obstruction and its cause (eg, inferior vena cava web, hypercoagulative state such as protein C or S deficiency, malignancy, leukemia, etc).[22] The management of BCS should therefore be highly individualized based on the clinical presentation, severity of liver failure, austerity of venous obstruction, underlying precipitating factors, and presence of HCC and cirrhosis.[2] TIPS has become the preferred treatment in selected BCS patients with signs of liver decompensation.[7] It may function as a temporizing measure to manage complications of portal hypertension (eg, portal hypertension) as a bridge to LT.[12]

Post-LT survival was comparable in BCS patients with or without prior TIPS. Post-LT survival in BCS at 5 and 10 y was 81.3% and 70.8% in the TIPS group compared with the no-TIPS group at 80.6% and 72.7% (P = 0.93). These data are consistent with prior studies showing that LT yields positive long-term outcomes in BCS patients.[12,21,23] Since the start of the MELD-era organ allocation system, outcomes for BCS patients have markedly improved, with a 3-y posttransplant survival of 84%.[9] Similarly, in another study, overall survival was 76%, 71%, and 68% at 1, 5, and 10 y, respectively.[15] Advances in the field of LT and adoption of the MELD score for deceased donor liver allocation may have improved survival following LT for BCS.[12] Prior studies gave TIPS a role as a temporizing strategy to treat complications of portal hypertension before LT in selected BCS patients.[7,24–26]

In our multivariate model, factors associated with increased mortality included Black/AA ethnicity. It is plausible that health inequities in the United States and its health system may be an underlying contributing factor to higher posttransplant mortality among BCS patients of Black/AA ancestry.[27] Examination and potential revision of health policies that may disadvantage Black/AA patients with BCS are needed in future studies. The inclusion of DRI as a major driver of post-LT mortality highlights the importance of donor factors for successful LT because the DRI reflects a combination of multiple donor factors that influence mortality.[28] Contrarily, diabetes is a common recipient-associated comorbidity in patients waiting for LT and is known to be a significant risk factor for post-LT mortality because of cardiovascular complications, infections, and renal failure.[29] Therefore, an association with post-LT mortality is expected.[30] Similarly, the length of hospital stay might reflect the degree of "sickness" before LT and/or complications that may arise following LT. Higher albumin at the time of transplantation was associated with reduced mortality risk in our multivariate model. Reduced albumin is a marker of cirrhosis and is already used in the Child-Pugh score to predict cirrhosis mortality.[31,32] Interestingly, neither

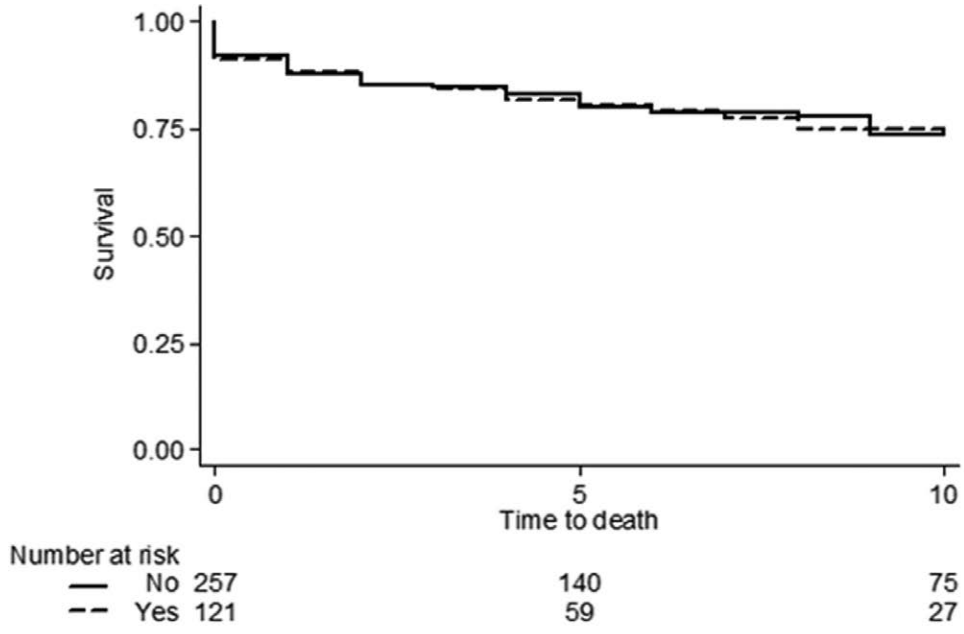

FIGURE 1. Post-LT survival in Budd-Chiari syndrome patients based on pre-LT TIPS status. LT, liver transplantation; TIPS, transjugular intrahepatic portosystemic shunt

TABLE 4.

Cox proportional hazard analysis of predictors of mortality among BCS liver transplant recipients

Characteristics	HR (95% CI)	*P*
Race (Black/AA vs White)	2.24 (1.38-3.64)	0.001
Diabetes	3.17 (1.62-6.21)	<0.001
LOS following LT (d)	1.32 (1.19-1.47)	<0.001
Albumin (g/dL)	0.66 (0.50-0.88)	0.004
DRI	1.44 (1.05-1.99)	0.03

Variables included in the model: Recipient characteristics: gender, race, ABO type, BMI, diabetes, HCC, HE, ascites, PVT, dialysis, TIPS, life support, status 1, MELD, sodium, creatinine, bilirubin, INR, albumin, wait time, and LOS posttransplantation. Donor characteristics: age, gender, BMI, total cold ischemic time, and DRI.

AA, African American; BCS, Budd-Chiari syndrome; BMI, body mass index; CI, confidence interval; DRI, donor risk index; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HR, hazard ratio; INR, international normalized ratio; LOS, length of hospital stay; LT, liver transplantation; MELD, Model for End-stage Liver Disease; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.

MELD nor prior TIPS showed a significant association with long-term survival after LT.

Next, we analyzed HCC patients with BCS. Regenerative nodules are frequently encountered in chronic BCS patients.[11] These lesions may range from a few millimeters to up to 4 cm in size and may be confused with HCC before LT.[11,33,34] On the other hand, HCC has been reported in 5% to 35% of BCS, with a 5-y cumulative incidence ranging from 4% to 17% across studies.[11,35–37] A recent study in the United States reported a 6.9% HCC incidence among BCS patients with a striking 5.4% change between 1998 and 2017.[38] In our cohort, the HCC frequency among BCS LT recipients was 10.3%. As expected, MELD was lower in BCS patients with HCC, and the wait time for LT was longer. HCC was not associated with shorter or longer survival after transplant. Explant data were available for 17 patients with HCC. Overall, 8 (47%) patients had no viable lesion on the explant. Three (17.8%) had multifocal HCC on the explant, whereas only 1 (5%) patient had a microvascular invasion. No patient had reported a poorly differentiated tumor. None of the explant livers showed satellite lesions or lymph node involvement (Table S4, SDC, http://links.lww.com/TXD/A474).

Moreover, we analyzed BCS patients who received LT as a status 1 listing and reported favorable long-term outcomes.[39] Patient survival following status 1 LT has shown steady improvement in recent years.[40] Patients with BCS can present with acute-on-chronic liver failure.[41] In our cohort, >12% of BCS patients were transplanted as status 1. Recently, LT for status 1 in BCS patients was found to be associated with favorable survival compared with BCS patients who were not in status 1.[42] Here, we show that patients receiving LT as status 1 have comparable survival compared with other BCS LT recipients. However, it is important to note that this may have been related to the small sample size of status 1 patients.

There are several limitations to this study. A notable limitation is the inability to draw causal relationships due to the retrospective study design. Moreover, the cause of BCS, the timing and details of the TIPS procedure, anticoagulation use, and the extent of clot burden in BCS patients are unclear. Furthermore, our analysis did not distinguish between transplant-related mortality and all-cause mortality. The analysis was limited to variables available in the OPTN/UNOS database. Other variables of interest that were not available to include in the analysis (eg, causes of BCS, TIPS characteristics) might potentially impact post-LT survival. Moreover, data on explant livers were available for only 17 of the 40 HCC cases, limiting the power of this subanalysis.

Despite these limitations, the study had several strengths. First, it had very few patient exclusion criteria. Second, it included a wide range of patient demographic and clinical characteristics in statistical modeling and controlled for several important confounders, including age, gender, race, and MELD score. Compared with previous studies, the present study had a more extended study period and a considerably larger number of patients with post-LT mortality outcome data; both likely achieved a higher level of internal and external validity than prior studies. Lastly, the study's large sample size combined with the representativeness of UNOS/OPTN data strengthens the generalizability of the findings to LT outcomes in the United States. Altogether, the strengths of this study are the extended timeframe of the analysis—spanning nearly 2 decades—and its analysis of the comprehensive national transplant database. Nevertheless, given the lack of published data or clinical guidelines, these findings might help provide a framework for recommendations in managing BCS patients.

In conclusion, BCS is a rare indication among LT recipients. Findings from this study demonstrate that BCS patients can achieve excellent long-term survival after LT. We found comparable post-LT survival among BCS patients with or without pretransplant TIPS. The timing of LT and TIPS is a complex decision and should be individualized on a case-by-case basis. Our findings suggest that LT can lead to excellent long-term survival. Future research should aim to evaluate LT success in BCS patients in the setting of improved interventional radiology techniques.

REFERENCES

1. Menon KVN, Shah V, Kamath PS. The Budd-Chiari syndrome. *N Engl J Med*. 2004;350:578–585.
2. Valla D-C. The diagnosis and management of the Budd-Chiari syndrome: consensus and controversies. *Hepatology*. 2003;38:793–803.
3. Gupta S, Blumgart LH, Hodgson HJ. Budd-Chiari syndrome: long-term survival and factors affecting mortality. *Q J Med*. 1986;60:781–791.
4. Tavill AS, Wood EJ, Kreel L, et al. The Budd-Chiari syndrome: correlation between hepatic scintigraphy and the clinical, radiological, and pathological findings in nineteen cases of hepatic venous outflow obstruction. *Gastroenterology*. 1975;68:509–518.
5. McCarthy PM, Heerden JA van, Adson MA, et al. The Budd-Chiari syndrome. Medical and surgical management of 30 patients. *Arch Surg*. 1985;120:657–662.
6. Sharma A, Keshava SN, Eapen A, et al. An update on the management of Budd-Chiari syndrome. *Dig Dis Sci*. 2021;66:1780–1790.
7. Garcia-Pagán JC, Heydtmann M, Raffa S, et al; Budd-Chiari Syndrome-Transjugular Intrahepatic Portosystemic Shunt Group. TIPS for Budd-Chiari syndrome: long-term results and prognostics factors in 124 patients. *Gastroenterology*. 2008;135:808–815.
8. Hayek G, Ronot M, Plessier A, et al. Long-term outcome and analysis of dysfunction of transjugular intrahepatic portosystemic shunt placement in chronic primary Budd-Chiari syndrome. *Radiology*. 2017;283:280–292.
9. Ulrich F, Pratschke J, Neumann U, et al. Eighteen years of liver transplantation experience in patients with advanced Budd-Chiari syndrome. *Liver Transpl*. 2008;14:144–150.
10. Dutkowski P, Oberkofler CE, Béchir M, et al. The model for end-stage liver disease allocation system for liver transplantation saves lives, but increases morbidity and cost: a prospective outcome analysis. *Liver Transpl*. 2011;17:674–684.
11. Moucari R, Rautou P-E, Cazals-Hatem D, et al. Hepatocellular carcinoma in Budd-Chiari syndrome: characteristics and risk factors. *Gut*. 2008;57:828–835.

12. Segev DL, Nguyen GC, Locke JE, et al. Twenty years of liver transplantation for Budd-Chiari syndrome: a national registry analysis. *Liver Transpl*. 2007;13:1285–1294.
13. Ringe B, Lang H, Oldhafer KJ, et al. Which is the best surgery for Budd-Chiari syndrome: venous decompression or liver transplantation? A single-center experience with 50 patients. *Hepatology*. 1995;21:1337–1344.
14. Campbell DAJ, Rolles K, Jamieson N, et al. Hepatic transplantation with perioperative and long term anticoagulation as treatment for Budd-Chiari syndrome. *Surg Gynecol Obstet*. 1988;166:511–518.
15. Mentha G, Giostra E, Majno PE, et al. Liver transplantation for Budd-Chiari syndrome: a European study on 248 patients from 51 centres. *J Hepatol*. 2006;44:520–528.
16. Srinivasan P, Rela M, Prachalias A, et al. Liver transplantation for Budd-Chiari syndrome. *Transplantation*. 2002;73:973–977.
17. Halff G, Todo S, Tzakis AG, et al. Liver transplantation for the Budd-Chiari syndrome. *Ann Surg*. 1990;211:43–49.
18. Darwish Murad S, Plessier A, Hernandez-Guerra M, et al; EN-Vie (European Network for Vascular Disorders of the Liver). Etiology, management, and outcome of the Budd-Chiari syndrome. *Ann Intern Med*. 2009;151:167–175.
19. Zeitoun G, Escolano S, Hadengue A, et al. Outcome of Budd-Chiari syndrome: a multivariate analysis of factors related to survival including surgical portosystemic shunting. *Hepatology*. 1999;30:84–89.
20. Langlet P, Escolano S, Valla D, et al. Clinicopathological forms and prognostic index in Budd-Chiari syndrome. *J Hepatol*. 2003;39:496–501.
21. Akamatsu N, Sugawara Y, Kokudo N. Budd-Chiari syndrome and liver transplantation. *Intractable Rare Dis Res*. 2015;4:24–32.
22. Hobbs KE. Budd-Chiari syndrome. *Lancet (London, England)*. 1992;339:115–116.
23. Pandey Y, Vijayashanker A, Chikkala BR, et al. Living donor liver transplant for Budd-Chiari syndrome without caval replacement: a single-center study. *Exp Clin Transplant*. 2021;19:799–805.
24. Shrestha R, Durham JD, Wachs M, et al. Use of transjugular intrahepatic portosystemic shunt as a bridge to transplantation in fulminant hepatic failure due to Budd-Chiari syndrome. *Am J Gastroenterol*. 1997;92:2304–2306.
25. Parekh J, Matei VM, Canas-Coto A, et al; Acute Liver Failure Study Group. Budd-Chiari syndrome causing acute liver failure: a multicenter case series. *Liver Transpl*. 2017;23:135–142.
26. Ochs A, Sellinger M, Haag K, et al. Transjugular intrahepatic portosystemic stent-shunt (TIPS) in the treatment of Budd-Chiari syndrome. *J Hepatol*. 1993;18:217–225.
27. Bratton C, Chavin K, Baliga P. Racial disparities in organ donation and why. *Curr Opin Organ Transplant*. 2011;16:243–249.
28. Flores A, Asrani SK. The donor risk index: a decade of experience. *Liver Transpl*. 2017;23:1216–1225.
29. Thuluvath PJ. When is diabetes mellitus a relative or absolute contraindication to liver transplantation? *Liver Transpl*. 2005;(11 Suppl 2):S25–S29.
30. John PR, Thuluvath PJ. Outcome of liver transplantation in patients with diabetes mellitus: a case-control study. *Hepatology*. 2001;34:889–895.
31. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646–649.
32. Bernardi M, Zaccherini G, Caraceni P. Pro: the role of albumin in pre-liver transplant management. *Liver Transpl*. 2019;25:128–134.
33. Sakr M, Abdelhakam SM, Dabbous H, et al. Characteristics of hepatocellular carcinoma in Egyptian patients with primary Budd-Chiari syndrome. *Liver Int*. 2017;37:415–422.
34. Oliveira EC, Duarte AGE, Boin IFSF, et al. Large benign hepatocellular nodules in cirrhosis due to chronic venous outflow obstruction: diagnostic confusion with hepatocellular carcinoma. *Transplant Proc*. 2010;42:4116–4118.
35. Kew MC, Hodkinson HJ. Membranous obstruction of the inferior vena cava and its causal relation to hepatocellular carcinoma. *Liver Int*. 2006;26:1–7.
36. Seijo S, Plessier A, Hoekstra J, et al; European Network for Vascular Disorders of the Liver. Good long-term outcome of Budd-Chiari syndrome with a step-wise management. *Hepatology*. 2013;57:1962–1968.
37. Takayasu K, Muramatsu Y, Moriyama N, et al. Radiological study of idiopathic Budd-Chiari syndrome complicated by hepatocellular carcinoma. A report of four cases. *Am J Gastroenterol*. 1994;89:249–253.
38. Alukal JJ, Zhang T, Thuluvath PJ. A nationwide analysis of Budd-Chiari syndrome in the United States. *J Clin Exp Hepatol*. 2021;11:181–187.
39. McDiarmid SV, Goodrich NP, Harper AM, et al. Liver transplantation for status 1: the consequences of good intentions. *Liver Transpl*. 2007;13:699–707.
40. Wiesner RH. MELD/PELD and the allocation of deceased donor livers for status 1 recipients with acute fulminant hepatic failure, primary nonfunction, hepatic artery thrombosis, and acute Wilson's disease. *Liver Transpl*. 2004;10:S17–S22.
41. Shalimar, Sharma S, Gamanagatti SR, et al. Acute-on-chronic liver failure in Budd-Chiari syndrome: profile and predictors of outcome. *Dig Dis Sci*. 2020;65:2719–2729.
42. Alukal JJ, Zhang T, Thuluvath PJ. Outcomes of status 1 liver transplantation for Budd-Chiari syndrome with fulminant hepatic failure. *Am J Transplant*. 2021;21:2211–2219.