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ORIGINAL ARTICLE

Recent outcomes of liver transplantation for Budd-Chiari syndrome: A study of the European Liver Transplant Registry (ELTR) and affiliated centers

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Abstract

Background and Aims: Management of Budd-Chiari syndrome (BCS) has improved over the last decades. The main aim was to evaluate the contemporary post-liver transplant (post-LT) outcomes in Europe.

Approach and Results: Data from all patients who underwent transplantation from 1976 to 2020 was obtained from the European Liver Transplant Registry (ELTR). Patients < 16 years, with secondary BCS or HCC were excluded. Patient survival (PS) and graft survival (GS) before and after 2000

Abbreviations: BCS, Budd-Chiari syndrome; ELTR, European Liver Transplant Registry; GS, graft survival; HAT, hepatic artery thrombosis; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MPN, myeloproliferative neoplasm; PS, patient survival; Re-LT, retransplantation.

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were compared. Multivariate Cox regression analysis identified predictors of PS and GS after 2000. Supplemental data was requested from all ELTR-affiliated centers and received from 44. In all, 808 patients underwent transplantation between 2000 and 2020. One-, 5- and 10-year PS was 84%, 77%, and 68%, and GS was 79%, 70%, and 62%, respectively. Both significantly improved compared to outcomes before 2000 ($p < 0.001$). Median follow-up was 50 months and retransplantation rate was 12%. Recipient age (aHR:1.04,95%CI:1.02–1.06) and MELD score (aHR:1.04,95%CI:1.01–-1.06), especially above 30, were associated with worse PS, while male sex had better outcomes (aHR:0.63,95%CI:0.41–0.96). Donor age was associated with worse PS (aHR:1.01,95%CI:1.00–1.03) and GS (aHR:1.02,95% CI:1.01–1.03). In 353 patients (44%) with supplemental data, 33% had myeloproliferative neoplasm, 20% underwent TIPS pre-LT, and 85% used anticoagulation post-LT. Post-LT anticoagulation was associated with improved PS (aHR:0.29,95%CI:0.16–0.54) and GS (aHR:0.48,95% CI:0.29–0.81). Hepatic artery thrombosis and portal vein thrombosis (PVT) occurred in 9% and 7%, while recurrent BCS was rare (3%).

Conclusions: LT for BCS results in excellent patient- and graft-survival. Older recipient or donor age and higher MELD are associated with poorer outcomes, while long-term anticoagulation improves both patient and graft outcomes.

INTRODUCTION

Budd-Chiari syndrome (BCS) is a rare vascular liver disease caused by the obstruction of the hepatic venous outflow tract.[1] This could be asymptomatic (15%–20%) but could also result in fulminant, (sub)acute or chronic liver failure.[1,2] BCS has an estimated incidence of 1 per 1 million per year and a prevalence of 11 cases per 1 million, respectively.[3] BCS is considered primary BCS when it is caused by an intravascular obstruction (ie, thrombosis), and secondary when it is caused by extrinsic compression of the veins (eg, by neighboring space-occupying lesions).[4] Primary BCS is associated with a broad spectrum of underlying pro-thrombotic disorders,[4] often in combined presence. If thoroughly investigated, a causal factor can be found in up to 85% of BCS cases, with an underlying myeloproliferative neoplasm (MPN) in almost 50%.[5] Given the severity of the disease and the underlying thrombophilia, maintenance anticoagulation forms the backbone of treatment. Currently, a stepwise strategy is followed, starting with anticoagulants and diuretics.[4,6,7] When pharmacological treatment is not sufficient, invasive derivative techniques, such as percutaneous transluminal angioplasty and TIPS should be attempted to restore blood flow or prevent portal hypertension-related complications. TIPS can also be used as a bridging therapy while waiting for liver transplantation (LT).[8] However, in 10%–20% of the severe BCS cases, LT is needed.[7] LT is indicated in the setting of acute liver failure, in the case of end-stage chronic BCS, the development of HCC, or when previous therapies have failed.[5–7]

Due to the rarity of the disease, only a handful of studies have studied the outcomes of LT for larger groups of patients with BCS.[5,6,9–20] The only European Liver Transplant Registry (ELTR) report dates back to 2006 and reviewed the outcome of 248 patients who underwent transplantation from 1988 to 1999. They reported a 1- , 5- and 10-year survival of 76%, 71%, and 68%, respectively.[11] A recent registry study of the United Network for Organ Sharing reported on 446 patients with BCS who underwent transplantation between 1998 and 2008 and found a 5-year survival of 82%.[12] This may indicate that survival has improved in recent years.

The main aim of the current study was to evaluate the contemporary patient- and graft-survival following LT for BCS in Europe between 2000 and 2020. Secondary objectives were to evaluate the indications for LT, the rate and indication for retransplantation,

prognostic factors for patient- and graft-survival, and the impact of TIPS, etiology, and anticoagulation on patient- and graft outcome

METHODS

The European Liver Transplant Registry (ELTR)

The ELTR database was searched by using the G-code for BCS on all patients who underwent transplantation from 1976 to 31, December 2020. The search was conducted on both primary and secondary/tertiary indications for LT. All patients above 16 years old with BCS as a primary indication for transplantation were included. If the secondary or tertiary indication included liver tumors (benign or HCC), polycystic liver disease, or other chronic liver diseases, secondary BCS was suspected and these patients were subsequently excluded. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. Due to the retrospective character of the study, no additional approval by the appropriate ethics and/or institutional review committee(s) was necessary. In compliance with the General Data Protection Regulation rules (https://gdpr-info.eu), all ELTR-affiliated centers are responsible for collecting informed consent from patients before registration. As a result, additional (written) informed consent for this study was waived.

Supplementary data from ELTR-affiliated centers

All ELTR-affiliated centers were contacted with a list of their patients (2000–2020) and asked to provide supplementary and updated follow up data. A questionnaire was created (Supplemental S1, http://links.lww.com/HEP/I259). The supplementary data was cross-checked with the original ELTR dataset. If the data showed that a patient complied with our exclusion criteria, the patient was subsequently excluded from further analyses. Newly reported patients who underwent transplantation at the ELTR-affiliated center, but not registered in the original ELTR database, were not included.

Data collection

The ELTR variables included demographical and clinical data at the time of LT as well as primary and secondary outcomes. If a unit variable was missing, it was standardized based on the value and/or reported unit from other patients who underwent transplantation at the same center. All causes of death and indications for retransplantation (re-LT) were individually categorized. The ELTR variable entitled "primary non-/dysfunction, defined as re-LT or death ≤ 7 or > 7 days" was relabeled as 'graft dysfunction,' including classic Primary nonfunction but also other causes of graft dysfunction occurring after 7 days. If serum creatinine, total bilirubin, dialysis status, and international normalized ratio (INR) were all available, the MELD score pre-LT was calculated.[21,22] The calculated MELD was cross-checked with the reported MELD score and was used instead if the difference was not more than 2.0 points from the reported MELD. All cases with a difference of more than 2.0 points were individually checked, and in consultation with a hepatologist (Sarwa Darwish Murad) the decision was made whether to use the original MELD or calculated MELD. If the INR was missing but the original MELD score was reported, the missing value was derived from the reported MELD. All cases with a calculated INR above 2 were individually checked. An INR score above 10 was assumed to be unreliable and therefore rounded to 10. Furthermore, to exclude the possibility that a therapeutic INR (due to unreported use of vitamin K antagonists) artificially increased the MELD score, we performed sensitivity analysis by first calculating an adjusted MELD-score in which INR was set to 1.0 and second, by calculating the MELD XI (ie, bilirubin, creatinine).[23] Finally, the Rotterdam BCS index (including encephalopathy, ascites, prothrombin time, and bilirubin),[24] Child-Pugh score,[25,26] and Clichy score (ascites, Child-Pugh score, age, and creatinine)[27] were calculated if the respective variables were available. Missing values were more common in patients who underwent transplantation before 2008.

Primary and secondary outcome

The primary outcomes were post-LT PS and GS. Outcomes and characteristics of patients who underwent transplantation before and after 2000 were compared to assess for an era effect. Secondary outcomes included posttransplant complications (ie, portal vein thrombosis [PVT], hepatic artery thrombosis [HAT]), cause of death, recurrence of BCS, and retransplantation rate.

Statistical methods

Continuous variables were described as mean with SD or as median with IQR if not normally distributed. Categorical data were presented as counts and (valid) percentages. To compare characteristics between patients who underwent transplantation before versus after the year 2000, parametric statistical tests (ie, two-tailed unpaired *t*-test) were used for normally distributed continuous data and nonparametric statistical tests (ie, Mann-Whitney

U test) were used if the data was not normally distributed. Categorical data was analyzed with the chi-square test.

Posttransplant PS and GS were assessed by using Kaplan Meier curves for the overall ELTR cohort and compared between patients who underwent transplantation before and after 2000. The remainder of the analyses were performed on the cohort after 2000. To rule out potential selection bias, patients from centers that provided supplementary data were compared to centers that did not, with regards to gender, median age, high-urgency status, median MELD score, type of donor and PS/GS.

Multivariable Cox proportional hazard models included a random intercept for the center to account for the possible correlation between patients from the same hospital. Furthermore, we corrected for the known differences in underlying etiology and relation with the outcome of BCS in eastern (ie, Turkey, Azerbaijan) as opposed to western ELTR countries.[28,29] Re-LT was included as a time-dependent covariate in the analysis for PS. The included variables were based on clinical relevancy and availability. In the sub-cohort of patients with supplementary center data, we included the covariates TIPS pre-LT, etiology and oral anticoagulation pre-LT and post-LT, type of donor, east versus west, re-LT, and year of LT. Lastly, given the issue of missing values, sensitivity analyses were performed in the Bayesian framework, which allowed simultaneously imputing missing values in covariates obtaining parameter estimates, and including more variables.[30] Furthermore, a potential nonlinearity of the effect of MELD using quadratic or cubic functions of MELD was investigated. Selected results from the Bayesian model were visualized using effect plots that show the expected survival probability across different values of a particular covariate for a (hypothetical) patient with reference values for all other variables. All statistical analyses were performed with SPSS statistical software version 28[31] and R version 4.2.2[32] with the help of the package JointAI (version 1.0.4).[30] p values < 0.05 were considered statistically significant.

RESULTS

ELTR data 1976–2020

According to the ELTR registry, 1157 patients with BCS underwent transplantation in 125 centers in Europe between 1976 and December 31, 2020. From these, 56 patients were excluded due to possible secondary BCS, resulting in n = 1101 eligible for analysis. Of these, 293 patients (27%) underwent transplantation before 2000, and 808 (73%) underwent transplantation between 2000 and 2020. Follow-up data was missing from 5 patients and were excluded from further survival analysis (Figure 1). Since 5 centers did not perform transplants for BCS after 2000, 120 of the 125 ELTR-affiliated centers were contacted for supplementary data. Of these, 44 centers (37%) provided updated data from 363 patients (45%), Supplemental S2, http://links.lww.com/HEP/I259. As shown in Figure 2, BCS comprises only a fraction (0.38–1.21%) of LTs performed each year in the ELTR region.[33]

Comparison between patients who underwent transplantation before and after 2000

Table 1 shows the characteristics of patients who underwent transplantation before and after 2000. After 2000, 60% were female, the median age was 37.2 years, and 30% were listed as high urgency (39% of whom reported HE). The overall 1-, 5- and 10-year PS before and after 2000 were 71%, 67%, and 61% versus 84%, 77%, and 68%, respectively ($p < 0.001$, Figure 3A). GS at 1-, 5- and 10-year was 64%, 58%, and 52% before 2000 versus 79%, 70%, and 62% after 2000 ($p < 0.001$, Figure 3B). Median follow-up after LT was 61 months [IQR 10–156]. Re-LT rate was lower after 2000 compared to before (12 vs. 19%, $p = 0.007$). As shown in Figure 3C, a clear era effect was present with improved survival per decade.

Patient- and graft-outcomes after 2000

In total, 219 (27%) patients died with a median time of 4.6 months [0–54] post-LT. In total, 100 patients (12%) needed a re-LT after a median time of 15 days [6–598], and 57% of the re-LTs were performed within the first month. Aside from missing/other causes, the main cause of death was infection (23.7%), followed by recurrence BSC (6.8%), and the main indication of re-LT was HAT (23%) followed by graft dysfunction (20%) and recurrence BCS (8%) (Figure 4).

Multivariable Cox regression analysis on the original dataset (Table 2) showed that older recipient age (aHR 1.04; 95% CI: 1.02–1.06), and donor age (aHR 1.01; 95% CI: 1.00–1.03), re-LT (aHR 6.13; 95% CI 3.48–10.80) and increased MELD-score at LT (aHR 1.04; 95% CI 1.01–1.06) were significantly associated with worse PS, whereas males had better survival (aHR 0.63; 95% CI 0.41–0.96). Increased donor age was the only independent predictor for worse GS (aHR 1.02; 95% CI 1.01–1.03). Similar predictors were identified (except from donor age and male gender for PS) when using the Bayesian approach with the imputation of missing variables, regardless of whether a linear or quadratic effect of MELD was assumed (Supplemental S3, http://links.lww.com/HEP/I259 and S4, http://links.lww.com/HEP/I259).

After categorizing the MELD and applying the same Cox model, a MELD above 30 was associated with a

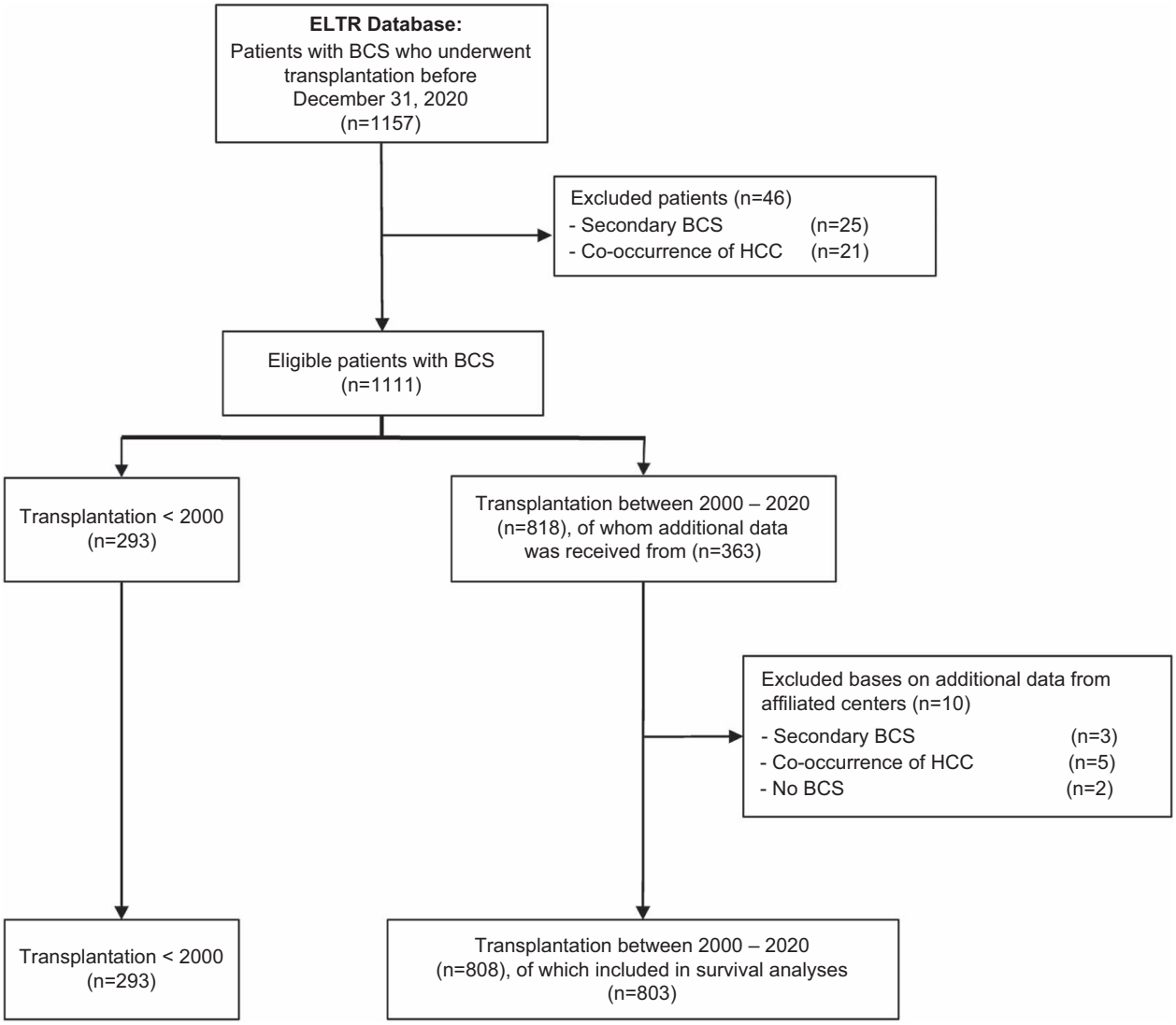


FIGURE 1 Flowchart of all included patients. Abbreviations: BCS, Budd-Chiari syndrome; ELTR, European Liver Transplant Registry.

significantly increased mortality (aHR 3.02; 95% CI 1.58–5.78; $p < 0.001$) compared to MELD 21-30 (aHR 1.02; 95% CI: 0.55–1.89), MELD 15–20 (aHR 1.24; 95% CI 0.76–2.02) and MELD < 15 (reference). Plotting the log hazard of MELD, a decrease in PS is seen for a MELD score of 20 and above, especially above 30 when assuming a quadratic effect. The expected survival at different MELD scores was almost identical

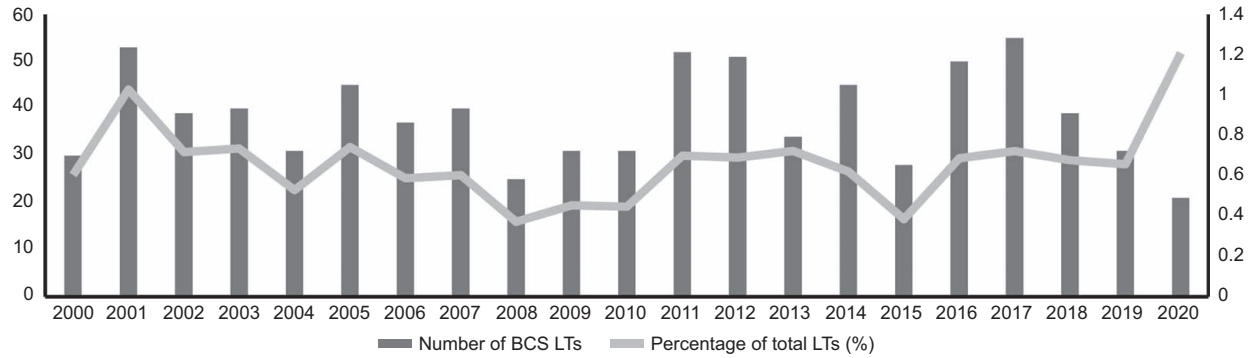


FIGURE 2 Number of patients who underwent transplantation with primary BCS per year. Dark grey-bars = absolute number of patients who underwent transplantation with BCS per year (left Y-Axis). Grey-line = percentage of the total patients who underwent transplantation within the ELTR region per year (right Y-axis). Abbreviations: BCS, Budd-Chiari syndrome; LT, liver transplantation.

TABLE 1 Comparison of baseline characteristics at the time of transplant between patients who underwent transplantation before versus and after 2000

	All patients (n = 1101)	Before 2000 (n = 293)	After 2000 (n = 808)	p[a]
Age (y)	37.0 [28.5–46.2]	35.5 [28.5–44.1]	37.2 [28.5–47.8]	0.086
Gender—female (n, (%))	696 (63.2)	209 (71.3)	487 (60.3)	< 0.001
Underlying etiology (n, (%))				
MPN (ie, PV, ET, PMF)	109 (32.7)	—	109 (32.7)	—
Other	69 (20.7)	—	69 (20.7)	—
Unknown	155 (46.5)	—	155 (46.5)	—
Missing (a)	768 (69.8)	—	475 (58.8)	—
Time on waiting list (d)	17.0 [3.0–99.0]	13.5 [2.0–54.5]	19.0 [3.0–123.0]	< 0.001
Follow up post-LT (mo)	61 [10–156]	151 [2–255]	50 [11–114]	—
Usage of OAC pre-LT - (n, (%))	212 (63.7)	—	212 (63.7)	—
Missing(a)	768 (69.8)	—	475 (58.8)	—
Clinical presentation at LT	—	—	—	—
Clinical ascites (n, (%))	—	—	—	< 0.001
None	173 (31.7)	36 (48.0)	137 (29.1)	—
Controlled with medication	200 (36.6)	31 (41.3)	169 (35.9)	—
Refractory	173 (31.7)	8 (10.7)	165 (35.0)	—
Missing (a)	555 (50.4)	218 (74.4)	337 (41.7)	—
Encephalopathy (n, (%))	—	—	—	0.475
None	416 (66.6)	57 (72.2)	359 (65.8)	—
Grade I-II	152 (24.3)	17 (21.5)	135 (24.7)	—
Grade III-IV	57 (9.1)	5 (6.3)	52 (9.5)	—
Missing(a)	476 (43.2)	214 (73.0)	262 (32.4)	—
High urgency listing (n, (%))	282 (30.3)	75 (32.6)	207 (29.5)	0.371
Missing (a)	169 (15.3)	63 (21.5)	106 (13.1)	—
TIPS pre-LT (n, (%))	65 (19.6)	—	65 (19.6)	—
Missing (a)	769 (69.8)	—	476 (58.9)	—
Dialysis twice a week (n, (%))	16 (2.8)	0 (0)	16 (3.3)	0.076
Missing (a)	522 (47.4)	200 (68.3)	322 (39.9)	—
MELD-score at LT	18 [13–24]	21 [15–33]	17 [13–24]	0.062
< 15	192 (33.7)	7 (25)	185 (34.2)	—
15–20	171 (30.1)	7 (25)	164 (30.3)	—
21–30	120 (21.1)	6 (21.4)	114 (21.1)	—
> 30	86 (15.1)	8 (28.6)	78 (14.4)	—
Missing (a)	532 (48.3)	265 (90.4)	267 (33.0)	—
Serum creatinine (umol/L)	80.7 [63.7–117.3]	88.5 [73.0–133.0]	79.6 [62.0–115.8]	0.006
Total bilirubin (umol/L)	43.8 [22.2–84.0]	50.0 [24.0–80.3]	42.8 [22.2–85.9]	0.579
Albumin (g/L)	31.7 (8.3)	32.3 (8.1)	31.6 (8.3)	0.607
INR	1.7 [1.4-2.4]	1.8 [1.5-2.9]	1.7 [1.4-2.4]	0.277
Prognostic Indices	—	—	—	—
Child-Pugh score (n, (%))	—	—	—	0.297
CP-A	33 (11.5)	1 (25.0)	32 (11.3)	—
CP-B	153 (53.3)	3 (75.0)	150 (53.0)	—
CP-C	101 (35.2)	0 (0)	101 (35.7)	—
Missing(a)	814 (73.9)	289 (98.6)	525 (65.0)	—
Rotterdam index (n, (%))	—	—	—	0.505
Class I	92 (24.9)	2 (50.0)	90 (24.7)	—
Class II	127 (34.4)	1 (25.0)	126 (34.5)	—
Class III	150 (40.7)	1 (25.0)	149 (40.8)	—

TABLE 1. (*continued*)

	All patients (n = 1101)	Before 2000 (n = 293)	After 2000 (n = 808)	p[a]
Missing (a)	732 (66.5)	289 (98.6)	443 (54.8)	—
Clichy score (n, (%))	—	—	—	0.674
</ = 5.4	275 (95.8)	4 (100)	271 (95.8)	—
> 5.4	12 (4.2)	0 (0)	12 (4.2)	—
Missing(a)	814 (73.9)	289 (98.6)	525 (65.0)	—
Donor characteristic	—	—	—	—
Age (y)	39.8 [25.7–52.8]	31.6 [22.3–45.7]	42.2 [28.4–54.6]	< 0.001
Gender—female (n, (%))	480 (44.8)	111 (40.1)	369 (46.4)	0.068
Missing(a)	29 (2.6)	16 (5.5)	13 (1.6)	—
Type of donor	—	—	—	< 0.001
DBD	928 (85.7)	277 (99.3)	651 (81.0)	—
DCD	14 (1.3)	0 (0)	14 (1.7)	—
Living	138 (12.7)	2 (0.7)	136 (16.9)	—
Domino	3 (0.3)	0 (0)	3 (0.4)	—
Missing(a)	18 (1.6)	14 (4.8)	4 (0.5)	—

Data is presented as mean (SD), median [P25-P75] or valid percentage, except for the percentages of the missing values (a).
[a]Difference between before and after 2000 was compared using Mann-Whitney *U* test (if not normally distributed), independent *t*-test (normal distribution), and chi Square test (categorical).
Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death; ET: essential thrombocytosis; LT, liver transplantation; MPN, myeloproliferative neoplasm; OAC, oral anticoagulation; PMF, primary myelofibrosis; PV, polycythemia vera.

for the different versions of the MELD score (ie, adjusted MELD and MELD-XI) (Supplemental S5, http://links.lww.com/HEP/I259).

The association between recipient age and PS appeared significantly incremental with an aHR of 1.84 (95% CI 1.02–3.31) for age 30–40, 2.33 (95% CI 1.26–4.33) for age 40–50, 3.65 (95% CI 1.95–6.81) for age 50–60 and the highest aHR of 4.64 (95% CI 1.85–11.65) for patients aged > 60 years (Supplemental figure S6, http://links.lww.com/HEP/I259). For donor age and PS, only donor age > 60 was significantly associated with worse outcomes (aHR 2.19; 95% CI 1.17–4.10). As for donor age and GS, donor age below 50 years was not significantly associated, whereas thereafter, an incremental increase was seen with aHR of 1.78 (95% CI 1.05–3.02) for age 50–60, and 2.79 (95% CI 1.64–4.75) for age > 60.

Supplementary data from ELTR affiliated centers

After re-applying exclusion criteria, supplementary data was received from 353 patients (44%). Besides differences in recipient female gender (56% vs. 64%, $p = 0.02$) and living donor LT (28% vs. 8%, $p < 0.01$), no differences in age (36.9 vs. 37.6, $p = 0.99$), MELD-score (17 vs. 18, $p = 0.64$), or high urgency listing (30% vs. 29%, $p = 0.66$) were present between this sub-cohort and those without supplementary data. Furthermore, there were no significant differences in the 1-, 5- and 10-year PS (86%, 79%, and 74% vs. 82%, 75%, and 64%, respectively, $p = 0.09$) and GS (81%, 73%, and 67% vs. 77%, 69%, and 57%, respectively, $p = 0.10$) between both cohorts. Also, the rate of re-LT was similar in both groups (10% vs. 14%, $p = 0.10$), all suggesting that this sub-cohort is a reasonable representation of the total population.

Data on the etiology of BCS was reported for 333 patients (94%), of whom 33% with myeloproliferative neoplasm (ie, polycythemia vera, essential thrombocytosis, or primary myelofibrosis). In total, 212 (64%) patients used oral anticoagulation pre-LT and 287 (85%) post-LT. TIPS was placed in 20% of the patients. In total, 32 of these patients (9%) developed HAT post-LT within a median time of 10 [2–70] days after LT, and 89% of HAT occurred within the first year. The frequency of HAT did not differ between patients with or without MPN (7.4% vs. 10.4%, $p = 0.39$) and living versus deceased donors (6.1% vs. 10.8%, $p = 0.18$). PVT post-LT occurred in 25 patients (7%) with a median time of 70 [1–511] days after LT. PVT frequency was similar in patients with or without MPN (9.3% vs. 6.3%, $p = 0.39$) and in living versus deceased donors (8.1% vs. 7.1%, $p = 0.74$).

Although there were no differences in frequency of HAT (9.1% vs. 11.5%, $p = 0.57$) or PVT (7.7% vs. 5.8%, $p = 0.63$) between patients who were initiated on long-term anticoagulation for prevention of recurrent BSC versus those who were not, it is important to note that 64% of all vascular complications (ie, 63% in HAT and 60% in PVT) developed while anticoagulation was already started. The majority of these patients were treated with oral vitamin K antagonists (60.8% in PVT and 45.8% in HAT), followed by low molecular weight heparin (21.7% and 50%, respectively) or direct oral anticoagulants (8.7% and 4.2%, respectively).

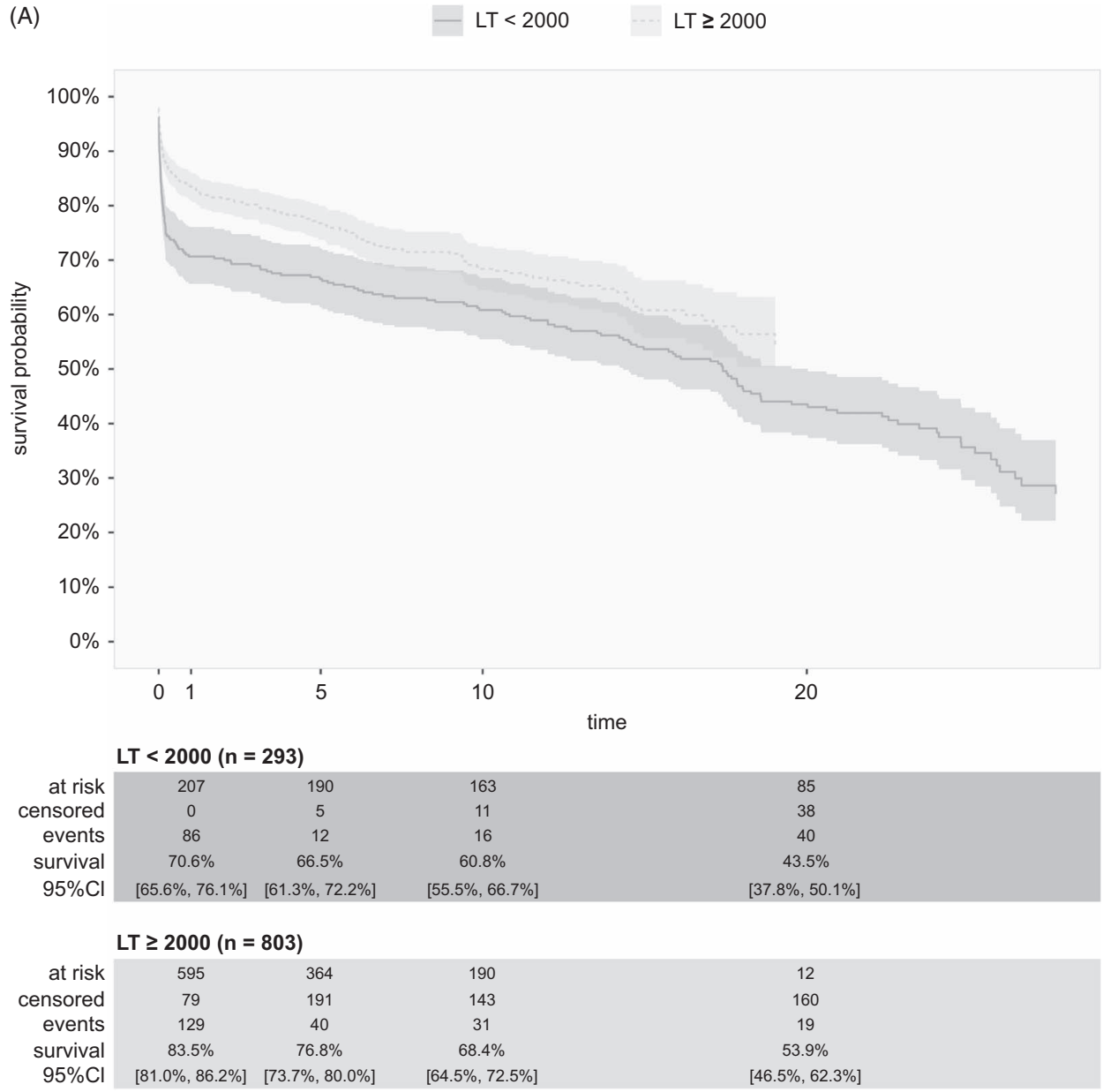


FIGURE 3 Comparison of patient- and graft survival between patients who underwent transplantation before and after 2000. (A) Overall PS post-LT, Log-rank: p = 0.001. (B) GS post-LT, Log-rank: p < 0.001 (C) Era effect PS (ie, per decade). Abbreviations: GS, graft survival; LT, liver transplantation; PS, patient survival.

Recurrent BCS was reported in 3.1% of the patients, with a median time of 2.11 [1.01–4.09] years after LT. Again, no differences were found among patients with or without maintenance anticoagulation (3.5% vs. 0%, $p = 0.17$), with or without MPN (1.9% vs. 3.6%, $p = 0.38$), and in living versus deceased donation (2.9% vs. 4.0%, $p = 0.60$).

Multivariate Cox analysis of the sub-cohort did not show an association between PS and underlying etiology or pre-LT TIPS placement after adjusting for recipient and donor age, gender, donor type, re-LT, east versus west, year of LT, and center effect (Table 3). Post-LT maintenance anticoagulation was the only independent factor associated with both improved PS (aHR 0.29; 95% CI 0.16–0.54) and GS (aHR 0.48; 95% CI 0.29–0.81). These results were similar (1) after the imputation of incomplete variables, whether or not a linear or quadratic effect of MELD was used (Supplemental S3, http://links.lww.com/HEP/I259 and S4, http://links.lww.com/HEP/I259); and (2) after excluding patients who died, underwent re-LT or were lost to follow up within the first days after LT (results not shown).

DISCUSSION

This study provides an updated analysis of 803 ELTR-registered patients with BCS who underwent transplantation in 120 affiliated centers since 2000, supplemented

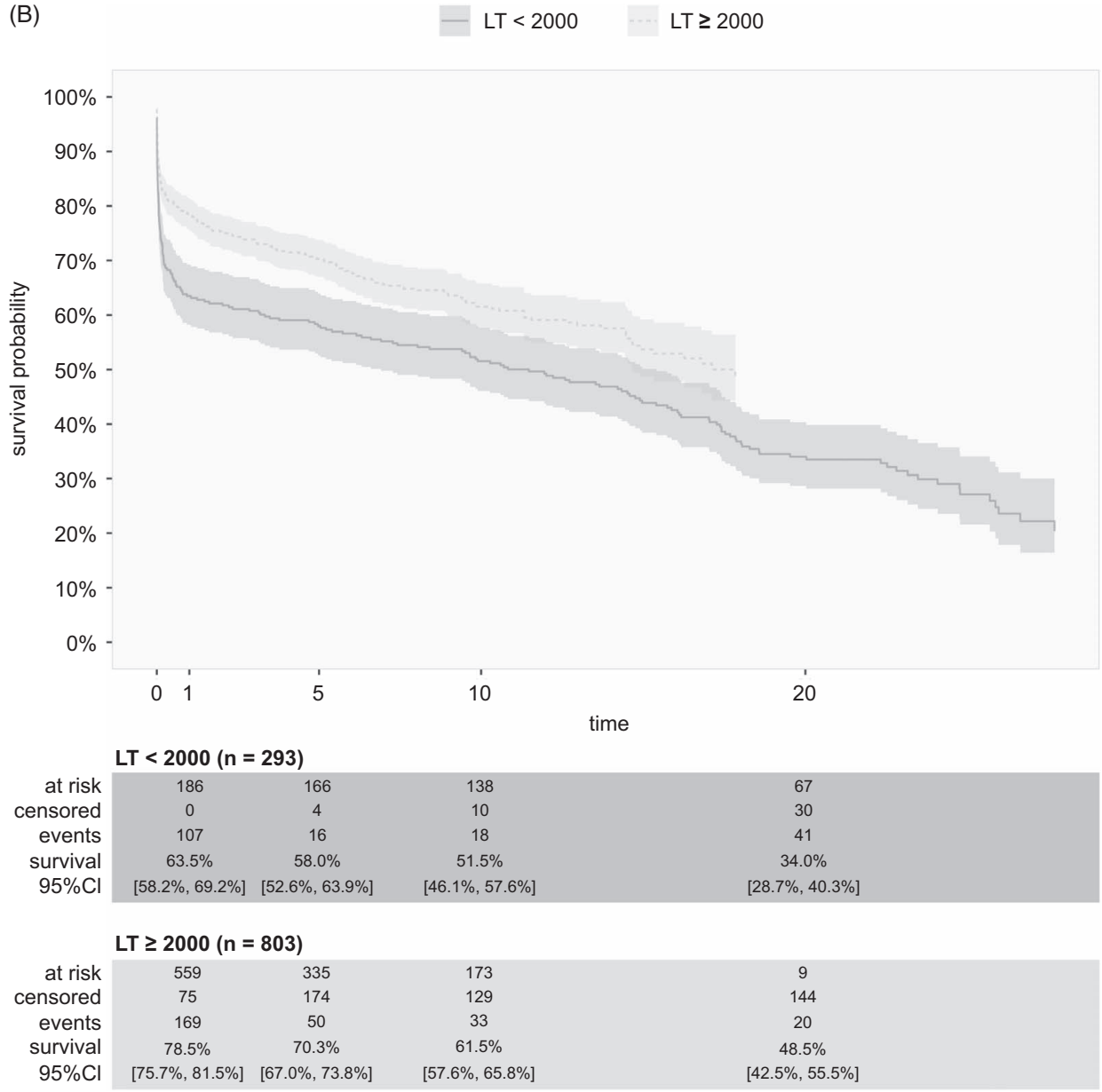
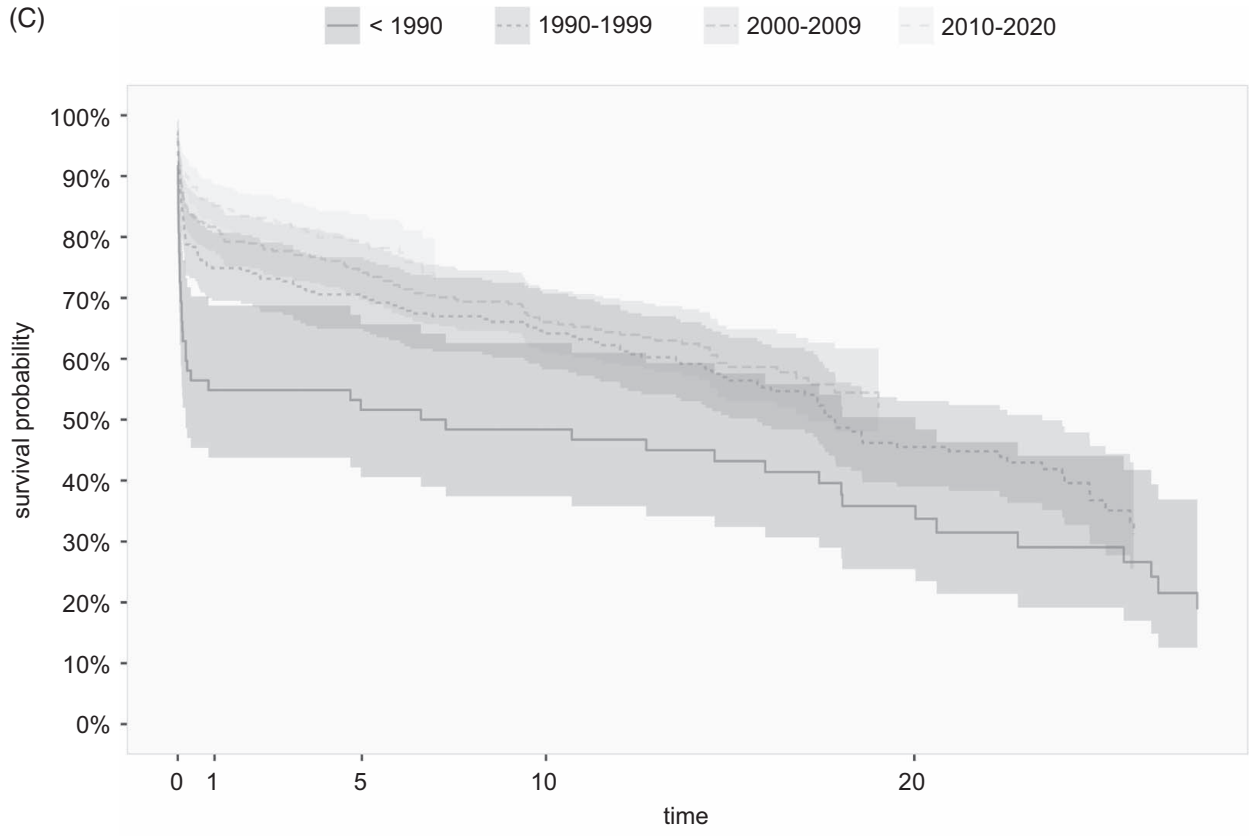


FIGURE 3 *(Continued).*

with BCS-specific data received from 44 centers (n = 353, 44%). In line with the rarity of the disease, BCS comprises only 1% of all LTs performed in the ELTR region on an annual basis. We found excellent mid- and long-term PS (77% at 5 y and 68% at 10 y) and GS (70% at 5 y and 62% at 10 y), which have significantly improved over time. Recipients with high age and MELD > 30 had the highest risk of mortality, and donor age was predictive of graft survival. In those with supplementary data, post-LT anticoagulation was the only additional factor independently associated with improved PS and GS.

The post-LT outcomes for BCS have significantly improved over the years, and a clear era effect is present. Our outcomes for LT before 2000 were slightly lower than the reported 1-,5- and 10-year survival of 76%, 71%, and 68%, respectively, in the ELTR study by Mentha et al[11]. This might be because the aforementioned study excluded patients before 1988 and these patients have worse survival, as shown in Figure 3C. Our results after 2000, however, are comparable to more recent studies.[9,11–13,34] The question arises why outcomes have improved over time and whether this is specific for BCS or merely an effect of general improvements in preoperative and postoperative management, surgical techniques, or immunosuppression, as noted for all LT indications.[35] A noticeable difference between patients who underwent transplantation before and after 2000 is the fact that 19.6% of the patients who underwent transplantation after 2000 received TIPS pre-LT,



< 1990 (n = 62)

at risk	34	32	29	17
censored	0	0	1	5
events	28	2	2	7
survival	54.8%	51.6%	48.4%	35.8%
95%CI	[43.8%, 68.7%]	[40.6%, 65.7%]	[37.4%, 62.6%]	[25.5%, 50.4%]

1990 - 1999 (n = 231)

at risk	173	158	134	68
censored	0	5	10	33
events	58	10	14	33
survival	74.9%	70.6%	64.2%	45.5%
95%CI	[69.5%, 80.7%]	[64.9%, 76.7%]	[58.2%, 70.7%]	[39.0%, 53.1%]

2000 - 2009 (n = 371)

at risk	272	224	174	12
censored	32	24	27	144
events	67	24	23	19
survival	81.7%	74.1%	66.0%	52.0%
95%CI	[77.8%, 85.7%]	[69.6%, 78.9%]	[61.1%, 71.4%]	[44.5%, 60.7%]

2010 - 2020 (n = 432)

at risk	323	140	16
censored	47	167	116
events	62	16	8
survival	85.1%	79.4%	73.0%
95%CI	[81.8%, 88.6%]	[75.3%, 83.8%]	[67.4%, 79.1%]

FIGURE 3 *(Continued).*

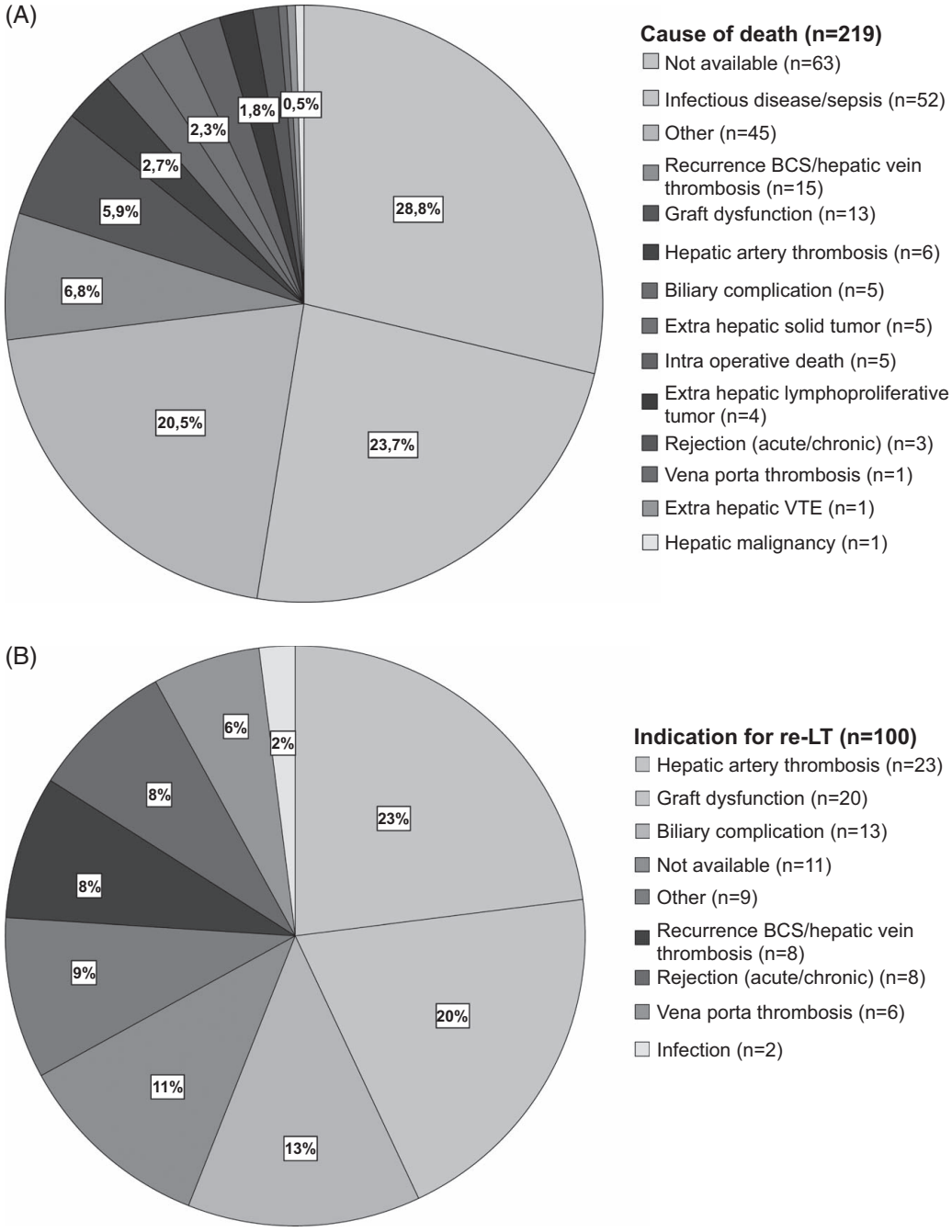


FIGURE 4 (A) Causes of death and (B) indication for retransplantation for patients with BCS who underwent transplantation after 2000. Abbreviations: BCS, Budd-Chiari syndrome; LT, liver transplantation.

whereas in the older series, only 4% of the patients who underwent transplantation before 2000 did.[11] However, TIPS did not have an independent impact on PS or GS. Some differences (eg, higher donor age and less donation after brain death LT) over time would point towards lower expected outcomes, but this may be counterbalanced by other factors such as increased use of post-LT anticoagulation, which was found as the only protective factor. This, the observed improvement in outcomes over time, may therefore be a combination of

TABLE 2 Results of multivariate Cox regression analysis (cohort 2000–2020)

	Patient survival (n = 480)				Graft survival (n = 480)			
	aHR	95% CI		p	aHR	95% CI		p
Recipient age	1.039	1.022	1.056	< 0.001	1.009	0.995	1.024	0.213
Gender (male)	0.628	0.410	0.960	0.032	0.761	0.534	1.084	0.130
MELD score at LT	1.038	1.012	1.064	0.003	0.945	0.617	1.449	0.796
High urgency status	0.699	0.410	1.193	0.190	0.950	0.618	1.458	0.813
Living vs. deceased donors	1.958	0.712	5.380	0.193	1.695	0.627	4.578	0.298
Donor age	1.014	1.001	1.028	0.033	1.021	1.010	1.033	< 0.001
Year of LT	0.940	0.898	0.984	0.008	0.981	0.945	1.018	0.307
East vs. West regions	1.985	0.732	5.387	0.178	1.299	0.502	3.360	0.590
Retransplant[a]	6.133	3.483	10.80	< 0.001	—	—	—	—

[a]Time-dependent covariate, including random intercept for the center.
Abbreviation: LT, liver transplantation.

general improvements in LT care combined with the increased use of anticoagulation in patients with BCS.

Re-LT was needed in 12%. Interestingly, 50% was performed within 15 days post-LT and most re-LT were due to transplantation-related causes being graft failure or HAT (the latter even encompassing 23% of all re-TL). Recurrent BCS was very rare. Indeed, the high prevalence of HAT (9%) following LT for BCS is striking and at the higher end of that reported in BCS (3%–7%) or other indications for LT (3%–9%).[10,17,36,37] In our series, we did not find a significant association between the type of donor (living vs. deceased), underlying MPN or long-term anticoagulation, and frequency of HAT or PVT post-LT in patients with BSC. It was interesting to observe however that the majority of the patients who developed HAT or PVT did so while on anticoagulation for the prevention of the recurrence of BCS. A case series from 2005 also reported a high incidence of vascular/hematologic complications in patients who underwent transplantation with BCS.[38] Although not previously explored, 1 potential explanation might be the hypercoagulable status of patients with BCS, which may also explain why those on anticoagulation after LT have improved GS. However, as said before, no differences in the prevalence of HAT or PVT between anticoagulation and nonanticoagulation use were found, but we lacked the power to explore this further. These observations do warrant further investigation.

Although other studies have suggested that MELD may be a suboptimal predictor for overall BCS outcomes,[39] our results showed that a higher MELD score pre-LT was associated with worse survival post-LT, especially for MELD > 30. This MELD effect is also described for other LT indications,[40–42] and may be explained by the higher perioperative morbidity in patients with high MELD. A known disadvantage of using MELD is that most patients with BCS use oral anticoagulation (ie, vitamin K antagonists), which increases INR and overestimates the actual MELD score. To minimize the possibility that MELD observations were indeed biased by therapeutically elevated INR, we replaced MELD with an adjusted MELD (with INR set at 1.0) and MELD-XI[23] and showed that estimates remained in the same order of magnitude as the original MELD score. Also, the effect of MELD remained when correcting for the nonlinearity. Several other prognostic indices are known for BCS (ie, Rotterdam index, Clichy score, Child-Pugh score); however, unfortunately the predictive effect of these could not be analyzed due to the high number of missing data on the presence and severity of ascites and HE.

The presence of MPN was found in a third of the patients. In line with the current literature,[4,5,19,20,43] MPN did not impact patient or graft survival in our study. Neither had TIPS placement impact on PS or GS, as described by Alqahtani et al[44]. Independent of the

TABLE 3 Results of multivariate Cox regression analysis for subgroup of patients with supplementary data

	Patient survival (n = 312)				Graft survival (n = 312)			
	aHR	95%CI		p	aHR	95%CI		p
Myeloproliferative neoplasm	0.979	0.558	1.717	0.941	0.828	0.522	1.312	0.421
TIPS pre-LT	1.348	0.704	2.584	0.368	1.427	0.841	2.421	0.187
OAC pre-LT	0.695	0.400	1.207	0.197	0.733	0.465	1.155	0.181
OAC post-LT	0.294	0.159	0.542	< 0.001	0.482	0.286	0.812	0.006

Notes: Adjusted for recipient and donor age, sex, donor type, re-LT, east vs. west, and year of LT, including random intercept for center.
Abbreviations: LT, liver transplantation; MPN, myeloproliferative neoplasm; OAC, oral anticoagulants.

above-mentioned, oral anticoagulants post-LT resulted in both improved PS and GS, which confirms the ongoing need for anticoagulation in these patients even after LT.

Our study has several limitations. First, inherent to using registry data, some BCS-specific factors (such as anticoagulation use) were not available, and the potential relevant risk factors for post-LT outcome, such as pre-LT PVT or TIPS, were not systematically collected. In an attempt to enrich the analyses focusing on BCS-specific factors, supplementary data was requested from all centers and obtained from 37%. Although we cannot completely exclude the possibility of selection bias, the comparison of those with and without supplementary data did not reveal any relevant confounders. Second, registry data generally lack granularity due to a high number of missing values. To overcome this, both complete case analyses and data imputation analyses were performed and compared. As shown in the Supplemental material, http://links.lww.com/HEP/I259, these outcomes were largely comparable, strengthening our conclusions. Third, as our study and the ELTR registry include only post-LT data, we did not have any data on patients on waitlists who did not undergo LT. As such, we could not answer other potentially relevant questions in the field, such as whether pre-LT TIPS prevents or delays LT. Another potential limitation is that patients with the co-occurrence of HCC were excluded. Although HCC is a known indication for LT for BCS, no distinction could be made from the registry data whether the BCS was complicated by HCC (eg, primary BCS) or caused by the compression from HCC (eg, secondary BCS), and hence it was considered an exclusion criterion. Therefore, this cohort does not perfectly represent all patients who undergo LT and have BCS. However, the number of patients with HCC (n = 26) was very low and would probably not have impacted the results. Strengths of our study include the fact that this is the largest and the most recent overview of patients with BCS who underwent transplantation investigating long-term patient and graft outcomes and that we attempted to add granularity to the data by requesting additional BSC-specific data from the individual centers.

In conclusion, in this largest study of outcomes of LT for BCS thus far, we show excellent long-term PS and GS, which have significantly improved since 2000. Older recipient age and higher MELD scores seem to be associated with decreased patient survival. Furthermore, treating patients with oral anticoagulants post-LT seems beneficial, in particular in light of a relatively high rate of HAT. Further research, including more detailed patient data, is warranted.

AUTHOR CONTRIBUTIONS

Edo Dongelmans: Acquisition of data, analysis, and interpretation of data, drafting the manuscript, statistical analysis; Nicole Erler: Analysis and interpretation of data, drafting manuscript, statistical analysis and advice; Sarwa Darwish Murad: Study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, study supervision; Wojiech G. Polak: Study concept and design, critical revision of the manuscript for important intellectual content; Silvio Nadalin: ELTR liaison person; Rene Adam: ELTR custodian; Vincent Karam: Data manager ELTR; Sezai Yilmaz, Claire Kelly, Jacques Pirenne, Koray Acarli, Michael Allison, Abdul Hakeem, Vijayanand Dhakshinamoorthy, Dzmitry Fedaruk, Oleg Rummo, Murat Kilic, Arno Nordin, Lutz Fischer, Alessandro Parente, Darius Mirza, William Bennet, Yaman Tokat, Francois Faitot, Barbara B. Antonelli, Gabriela Berlakovich, David Patch, Frederik Berrevoet, Marija Ribnikar, Theophile Gerster, Eric Savier, Salvatore Gruttadauria, Bo-Göran Ericzon, Andrés Valdivieso, Valentin Cuervas-Mons, Baltasar Perez Saborido, Roland Croner, Luciano De Carlis, Giulia Magini, Roberta Rossi, Irinel Popescu, Laze Razvan, Stefan Schneeberger, Hans Blokzijl, Laura Llado, Miguel Angel Gomez Bravo, Christophe Duvoux, Vladimír Mezjlík, Gabriel C. Oniscu, Kelsey Pearson, Murat Dayangac, Valerio Lucidi, Olivier Detry, Fernando Rotellar, and Caroline den Hoed: Acquisition of supplementary data, (in order of number of cases) and critical revision of the manuscript for important intellectual content.

PRESENTATIONS

This study was presented at the International Liver Transplant Society annual congress 2022 – Istanbul, Turkey; O-047.

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CONFLICTS OF INTEREST

Michael Allison received grants from GlaxoSmithKline. David Patch is on the speakers' bureau for Gore. Stefan Schneeberger consults for Atara and Nefro Health. He is on the speakers' bureau for AstraZenica, Chiesi, OrganOx, and Xvivo. He received grants from Bridge to Life, Chiesi, Neovii, Organ Recovery, Pierre Fabre, and Sandoz. Christophe Duvoux advises Biotest and Ophiomic. Caroline den Hoed consults for Abacus and Takeda. She received grants from Chiesi and Orphalan. The remaining authors have no conflicts to report.

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