 doi:10.20944/preprints202110.0012.v1

TITLE PAGE

Living Donor Liver Transplantation for Budd-Chiari Syndrome: A Propensity Score-Matched Analysis

Gunasekaran V, Reddy MS, Rammohan A, Shanmugam N, Thiruchunapalli D, Kanagavelu RG, Kaliamoorthy I, Rela M

The authors of the above manuscript are:

Dr.Vasanthakumar Gunsekaran MCh[1] Email: Vasanth_smc@yahoo.co.in

Dr.Mettu S Reddy FRCS[2] Email: smettu.reddy@gmail.com

Dr. Ashwin Rammohan FRCS[1], Email: ashwinrammohan@gmail.com

Dr.Naresh Shanmugam FRCPCH[3] Email: drnareshps@googlemail.com

Deepashree Thiruchunapalli Email[4]: deepashree2003@gmail.com

Dr.Rathnavel G Kanagavelu FRCA[5] Email:gkrathnavel@gmail.com

Dr.Ilankumaran Kaliamoorthy FRCA[5] Email:ilan.kaliamoorthy@gmail.com

Prof.Mohamed Rela FRCS[1] Email: mohamed.rela@gmail.com

1. Institute of Liver Disease & Transplantation, Dr.Rela Institute & Medical Centre, Bharath Institute of Higher Education & Research, Chennai, Tamil Nadu, India.
2. Institute of Liver Disease & Transplantation, Gleneagles Global Health City, Chennai, Tamil Nadu, India
3. Department of Paediatric Hepatology, Dr.Rela Institute & Medical Centre, Bharath Institute of Higher Education & Research, Chennai, Tamil Nadu, India
4. Department of Interventional Radiology, Dr.Rela Institute & Medical Centre, Bharath Institute of Higher Education & Research, Chennai, Tamil Nadu, India

5. Institute of Critical care and Anaesthesiology, Dr.Rela Institute & Medical Centre, Bharat Institute of Higher Education & Research, Chennai, Tamil Nadu, India

Conflict of Interest Statement: The above doctors have no conflicts of interest or financial ties to disclose

Data Availability Statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions: Conceptualization, Vasanthakumar Gunasekaran and Mettu Reddy; Data curation, Rathnavel Kanagavelu and Ilankumaran Kaliamoorthy; Formal analysis, Vasanthakumar Gunasekaran, Mettu Reddy, Naresh Shanmugam, Deepashree Thirchunapalli and Mohamed Rela; Investigation, Vasanthakumar Gunasekaran; Methodology, Ashwin Rammohan and Naresh Shanmugam; Project administration, Ilankumaran Kaliamoorthy; Resources, Naresh Shanmugam, Deepashree Thirchunapalli, Rathnavel Kanagavelu and Ilankumaran Kaliamoorthy; Supervision, Mohamed Rela; Visualization, Deepashree Thirchunapalli; Writing – original draft, Mettu Reddy, Ashwin Rammohan and Rathnavel Kanagavelu; Writing – review & editing, Ashwin Rammohan and Mohamed Rela.

Corresponding Author:

Dr. Ashwin Rammohan MCh, FRCS, FACS

The Institute of Liver Disease & Transplantation, Dr.Rela Institute & Medical Centre, Bharath Institute of Higher Education & Research, CLC Works Road, Chennai, India 600044

Email id: ashwinrammohan@gmail.com

 doi:10.20944/preprints202110.0012.v1

Abbreviations:

AKI – Acute Kidney injury; APLA – Antiphospholipid antibody syndrome; AT – Anti-Thrombin; BCS - Budd-Chiari Syndrome; BMI – Body mass index; BSI – Blood stream infection; CECT – contrast enhanced computer tomography; CRRT – Continuous Renal Replacement therapy; CT – computer tomography; DDLT – Deceased Donor Liver Transplantation; EAD – Early allograft dysfunction; GRWR – Graft recipient weight ratio; HCC – Hepatocellular Carcinoma; HLH – Hemophagocytic Lymphohistiocytosis; HPS – Hepato-Pulmonary Syndrome; HV – Hepatic vein; HVOT – Hepatic venous outflow obstruction; INR - International Normalization Ratio; IVC – Inferior Vena Cava; LDLT – Living Donor Liver Transplantation, LT – Liver transplantation; MELD – Model for End-stage Liver Disease; MOVC – Membranous obstruction of vena cava; MPS - Myeloproliferative syndrome; PVT – Portal Vein Thrombosis; PSM - Propensity Score Matching; PTBD – Percutaneous transhepatic biliary drainage; QQ - quantile-quantile; RHV – Right Hepatic Vein; SBP – Spontaneous Bacterial Peritonitis; TIPSS – Trans-jugular Intrahepatic portosystemic shunt

 doi:10.20944/preprints202110.0012.v1

ABSTRACT

Introduction: There are unique technical and management challenges associated with living donor liver transplantation (LDLT) for Budd-Chiari Syndrome (BCS). The outcomes of LDLT for BCS in comparison to other indications remains unclear and warrants elucidation.

Methods: Data of 24 BCS patients who underwent LDLT between January 2012 and June 2019 were analyzed. There were 20 adults and 4 children. The early and long-term outcomes of adult LDLT BCS patients were compared to a control group of LDLT patients for other indications and matched using propensity scoring methodology.

Results: Primary BCS was observed in 22(91.7%) patients. Caval replacement was performed in 7(29.1%) patients. Early and late hepatic venous outflow tract (HVOT) complications were seen in 1(5.5%) and 3(16.7%) patients. Preoperative acute kidney injury was identified as a risk factor for mortality in the BCS cohort (p =0.013). On comparison, BCS recipients were younger with fewer comorbidities, more large volume ascites and higher rates of PVT. They also had longer cold ischemia time, increased blood loss and transfusion requirements, increased hospital stay, and higher late outflow complications. The 1-year and 3-year survivals were similar to non-BCS cohort (84.2% vs 94% and 70% vs 91.9%, respectively, log rank test p=0.09).

Conclusion: LDLT is remains a good option for symptomatic BCS who have failed non-transplant interventions. The clinical and risk factor profile of BCS recipients is distinct from non-BCS recipients. By following an algorithmic management protocol, we show on propensity-score matched analysis that outcomes of LDLT for BCS are similar to non-BCS indications.

Keywords: Budd-Chiari syndrome; Living donor; Liver transplantation; Propensity score-Matched Analysis; Outcomes

 doi:10.20944/preprints202110.0012.v1

1. INTRODUCTION:

Budd-Chiari syndrome(BCS) is a rare veno-occlusive disorder characterized by hepatic venous outflow obstruction in the absence of coexisting cardiac disease.[1] Liver transplantation(LT) is necessary in about 10-20% of BCS patients when non-transplant options are not feasible.[2] LT in BCS poses special problems due to technical difficulties during the operation in the form of the massively enlarged congested liver with severe portal hypertension and dense retroperitoneal fibrosis; all of which causing increased blood loss during the hepatectomy phase. The postoperative management is challenging due to the balance between good hemostasis and therapeutic anticoagulation necessary in these recipients. In the long term, there are issues of vascular thrombosis, disease recurrence, and graft failure.[3,4] Deceased donor liver transplantation (DDLT) for BCS has been reported with a good outcome with 5-year survival ranging from 65% to 95%.[5,6,7] Living donor liver transplantation (LDLT) in BCS is associated with additional technical challenges. Here, the lack of availability of retrohepatic vena cava in the graft for caval anastomosis and the hepatic venous reconstruction on a diseased recipient cava poses special technical issues.

LDLT for BCS was first reported in a child in 1999.[8] The majority of publications are in the form of individual case reports and a few case series.[9,10] There is no data comparing the outcomes of LDLT for BCS with non-BCS patients.

We present, in one of the largest single centre series to-date, the short and long-term results of patients who underwent LDLT for BCS. We also compare the outcomes with a Propensity Score Matched (PSM) non-BCS LDLT cohort.

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2. MATERIALS AND METHODS:

The study was conducted in accordance with the principles of the Declaration of Helsinki (2008) and 'good clinical practice' guidelines after approval by the Institutional ethics committee (ECR/1276/Inst/TN/2019/001 dated:22nd Feb 2020). Review of a prospectively collected database of all adults and children with BCS who underwent LDLT between January 2012 and June 2019 was performed. It was supplemented by inpatient and outpatient clinical records, along with subsidiary databases of radiological and endoscopic interventions.

2.1 *Diagnosis & Evaluation for LT:*

The diagnosis of BCS was based on characteristic clinical presentation and evidence of obstructed hepatic venous outflow on imaging. Based on the presentation, BCS patients were classified into acute, sub-acute, and chronic forms. All patients were evaluated for hereditary and/or acquired conditions of thrombophilia and if needed, had a bone marrow biopsy to identify any underlying prothrombotic condition. Those with no identifiable cause on evaluation were considered as idiopathic. All patients underwent a triple phasic CECT of the abdomen with an additional 3 minutes delayed imaging to assess the status of the IVC, hepatic veins, and the Porto-mesenteric venous system. Any previously placed caval or hepatic venous stents and/or TIPSS were documented.

The management protocol was based on the presence of liver failure, severity of portal hypertension, and feasibility of non-transplant interventions. (Figure 1) LT was offered to patients with acute or sub-acute BCS with significant liver dysfunction, decompensated chronic liver disease, HCC within UCSF criteria, or other indications such as severe hepatopulmonary syndrome. All patients were discussed in a multidisciplinary team meeting and approved for

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transplantation. LDLT was the preferred option. Patients without suitable donors were listed for DDLT. Two patients of IVC leiomyosarcoma with secondary BCS and subacute liver failure underwent LDLT after a detailed discussion with the patient and family regarding risks and benefits. All patients received ABO compatible grafts.

Our donor evaluation protocol has been described in detail previously.[11] Donors with a functional liver remnant less than 30% were excluded. All potential donors underwent routine screening for procoagulant conditions.

2.2 Recipient surgery:

In BCS recipients, the enlarged congested liver causes difficulty in liver mobilization and division of triangular ligaments in the initial phase of operation. Early hilar dissection and hepatic artery ligation reduced liver congestion significantly. All visible lymphatic channels were ligated to reduce the excess fluid loss from these open lymphatic channels. When portal vein thrombosis (Yerdel's grading)[12] was present, thrombectomy was attempted to obtain satisfactory portal inflow. In patients with porto-mesenteric venous thrombosis, a mesenterico-portal jump graft or a left reno-portal anastomosis was performed.

The native recipient cava was preserved whenever possible and used for implantation. Any fibrotic areas around hepatic venous orifices were excised to have healthy caval margins for implantation. If necessary, inferior vena cava (IVC) was cross-clamped to inspect its interior and any web or bands present within the lumen were excised. Veno-venous bypass was not performed in any of the cases. When in doubt, a careful controlled digital assessment of cavo-atrial junction was performed to identify stenotic areas in the supra-hepatic cava and cavo-atrial junction. The cavo-atrial junction was accessed trans-abdominally via the diaphragm. The cava was resected, if

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it was chronically thrombosed, stenotic or when prior stenting procedures had thinned out the caval wall. Neo-cava was constructed using deceased donor cava or by conjoint venoplasty of two deceased donor iliac veins. A right lobe graft was implanted on the neo-cava in an anatomical location(Figure 2). In patients with thrombosed cava receiving left lobe or left lateral segment grafts, the graft was implanted directly onto the cavo-atrial junction.

2.3 Post-Operative Management:

Patients had daily Doppler studies to assess vascular patency for the first five days and then based on clinical need, until discharge. Screening Doppler ultrasound was performed during routine outpatient appointments to assess vascular patency. CT was not routinely used for screening. All patients transplanted for BCS received full anticoagulation with low molecular weight heparin in the early postoperative period, which was converted to oral Warfarin before discharge with a target international normalization ratio(INR) of 2.0 to 3.0. Anti-platelet therapy was started concomitantly for all patients, and both these medications were continued life-long.

Induction immunosuppression was not used for any patient. All patients received methylprednisolone intra-operatively during the anhepatic phase. Standard immunosuppression consisted of tacrolimus and steroids and mycophenolate mofetil was used selectively for patients assessed as a higher risk for rejection. The dose of prednisolone was gradually tapered over 3 months and the tacrolimus level was targeted between 6-9 ng/ml during the initial 6 months and adjusted to 4-6 ng/ml subsequently.

2.4 Definitions:

Pre-operative renal dysfunction was defined as serum creatinine greater than 1.5mg/dl at the time of transplant with no evidence of chronic kidney disease. Post-operative acute kidney

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injury(AKI) was defined as serum creatinine greater than 1.5mg/dl or an increase greater than 0.3 mg/dl within 48 hours or urine volume < 0.5 ml/kg/h for more than 6 hours.[13] Postoperative bleeding was defined as needing greater than three packed red blood cell transfusions in the postoperative period. Early allograft dysfunction(EAD) was defined as bilirubin ≥10mg/dL on day 7, INR ≥1.6 on day 7, and alanine or aspartate aminotransferases >2000 IU/L within the first 7 days.[14] Prolonged ascitic drainage was defined as more than 1000 ml ascitic drainage after 14 days of index surgery.

2.5 Statistical Analysis:

Data regarding patient demographics, clinical presentation, disease severity, peri-operative events, postoperative course, and early and long-term survival were analyzed. Descriptive methods were used to present data for the entire BCS cohort. Data is presented as mean(Standard Deviation) or median(interquartile range) for continuous variables and number(percentage) for discrete variables. Cox-regression analysis was used to identify risk factors for overall mortality within the BCS cohort.

Perioperative outcomes and survival of adult BCS cohort were compared with the non-BCS adult LDLT cohort. Preliminary analysis showed significant differences in covariates between the two groups. Propensity score matching was used to improve the matching of relevant co-variates.[15] Briefly, logistic regression analysis was performed to calculate a propensity score for each LDLT recipient using recipient age, recipient gender, donor age, MELD at transplantation, and final graft-recipient weight ratio as covariates. Co-variates were selected if they were significantly different between the two groups (recipient age, final GRWR) or were considered relevant to predict postoperative outcomes based on published LDLT literature and our unit

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experience (pre-operative MELD, recipient gender, donor age). After calculating propensity score, the nearest neighbor matching algorithm without replacement was used to select up to three matched controls for each BCS recipient, with a caliper width limit of 0.2.[16] Jitter plots and normal quantile-quantile(QQ) plots were performed to confirm that the BCS and control groups were well matched(Figure 3). The BCS and control groups were then compared using standard statistical tests. Unpaired Student T-test or Mann-Whitney U test was used to compare continuous variables, while the Chi-square test or Fisher exact test was used to compare discrete variables between the BCS and control cohorts. Kaplan-Meier curves were used to estimate actuarial survival rates and the log-rank test was used to compare survival between two groups. A two-sided p-value of less than 0.05 was considered statistically significant. The propensity scores calculation and selection of matched cohort was performed using R(R Foundation for Statistical Computing, Vienna, Austria) version 4.0.0 with the Matchlt package.[17] SPSS version 26(SPSS, Chicago, IL, USA) was used for the rest of the statistical analysis.

3. RESULTS:

During the study period, 1386 liver transplants were performed including 1050(75.8%) LDLTs and 336(24.2%) DDLTs. Two patients underwent DDLT for BCS and were not included in this analysis. Twenty-four patients(2.3%) underwent LDLT for BCS. There were 20 adults and 4 children. Patient demographics, clinical features, and pre-operative features are presented in Table 1.

3.1 Peri-Operative Details (Table 1 & 2)

3.1.1 Adults Recipients (N=20)

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Eighteen patients(90%) had primary BCS with an underlying procoagulant condition identified in eight patients. Ascites needing regular large-volume paracentesis and jaundice were the most common symptoms. All patients had Child B or C cirrhosis with a preoperative diagnosis of HCC in 2 patients. Six patients had undergone prior percutaneous or surgical decompression procedures and were referred for transplantation due to persistent/recurrent symptoms. The median Rotterdam score was 1.1 with 9 patients (37.5 %) in class III category. Pre-operative PVT was identified in 6 patients of whom 3 had high-grade PVT (Yerdel's grade 3 in 1 and grade 4 in 2). Two adult patients(40 years and 23 years) underwent LDLT for unresectable IVC leiomyosarcoma obstructing all three hepatic veins causing secondary BCS with liver failure.

The native cava could be preserved in 12(60%) adult recipients. Amongst these 12 patients, luminal webs needing web excision and cavo-plasty were identified in 3 patients. Two had webs in the supra-hepatic cava which were managed by excision and caval repair- primarily in one patient and using a vein patch in the other. A fibrotic web at the origin of the RHV in another patient was excised. IVC replacement using a neo-cava reconstruction was required in 7 patients undergoing right lobe LDLT(deceased donor vein in 6 and Dacron graft in one patient). One patient with thrombosed cava underwent left lobe LDLT with excision of native cava and a direct hepatic venous-right atrial anastomosis.

Portal venous thrombectomy was successful in three patients with PVT. Mesenterico-portal jump graft was required in one patient, while two patients needed the left reno-portal anastomosis to establish the portal inflow. Arterial reconstruction was standard in all patients except one adult who needed a vascular interposition graft. Biliary drainage was through a duct to duct anastomosis in 15 patients and a Roux-en Y reconstruction in 5 patients.

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3.1.2 Pediatric recipients (n=4):

The median age of children transplanted for BCS was 2 years(range 1- 6yrs). All had primary BCS with no identifiable prothrombotic disorder. One child had undergone multiple pre-operative hepatic vein venoplasties and was transplanted for liver decompensation with moderate HPS. Children received left lateral segment graft (n=3) or left lobe graft (n=1) and all underwent standard implantation to native cava. Roux-en Y biliary reconstruction was performed in 3 children.

3.2 Early Morbidity And Mortality (Table 2):

Major morbidity (Clavien-Dindo grade 3b/4) was seen in 5(20.8%) patients. Postoperative bloodstream infections (BSI) were seen in 8 patients(33.3%). AKI was seen in 7 patients(29.2%) in the postoperative period, 2 of which required CRRT. Three patients(12.5%) developed early bile leaks, 2 were managed with ERCP and stenting and one underwent percutaneous transhepatic biliary drainage (PTBD). Chyle leak was seen in 3 patients(12.5%) and was managed conservatively with a fat-free diet.

Reoperation was required in 3 patients(12.5%). One adult patient was re-explored for middle hepatic vein (MHV) thrombosis on day 5 and another adult was re-explored twice for intra-abdominal bleeding. A child required diaphragmatic hernia repair in the early postoperative period. Five patients(20.8 %) required re-admission within 90 days. The 90-day mortality of the entire BCS cohort was 12.5%(3/24). One patient developed early HVOT due to residual supra-hepatic caval stenosis needing an IVC stent on 1st postoperative day. He developed EAD, BSI and died. Another patient developed a large graft parenchymal hematoma following a percutaneous graft biopsy complicated by severe thrombocytopenia, EAD and multi-organ dysfunction

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syndrome. The third patient underwent a transplant for BCS with grade 4 PVT needing reno-portal inflow. He was re-explored twice for bleeding, developed AKI and sepsis and died after 46 days. There was no pediatric mortality in this series.

*3.3 Late Morbidity & Mortality (Table 2)**:***

The median follow-up was 23 months(0.5 – 103 months). The 1-year, 3-year survival and 5-year actuarial survival among BCS patients were 83.3 %, 71.3% and 71.3% respectively(Figure 4A). Three adult patients(12.5%) developed late hepatic venous obstruction. One patient developed graft RHV thrombosis, 18 months after transplant. He had stopped his anti-coagulants and presented with recurrent ascites and graft dysfunction. Anticoagulation was restarted and he underwent trans-jugular intrahepatic portosystemic shunt(TIPSS) with complete resolution of symptoms. Another patient with neo- cava reconstruction developed caval stenosis with ascites 6 months after transplant. He underwent neo-cava stenting with the resolution of symptoms. Another patient with a neocava developed asymptomatic RHV stenosis diagnosed on screening ultrasound 11 months after transplant. She was managed with venoplasty and is currently well. Anastomotic biliary strictures were seen in 3(12.5%) patients. All were successfully managed with Roux-en Y hepaticojejunostomy. One pediatric recipient developed recurrent diaphragmatic hernia with intestinal obstruction 33 months after LDLT. She underwent emergency laparotomy and repair with good recovery.

Three adult patients died during the follow-up period. One succumbed to intracranial bleeding after 13 months possibly due to inadvertent warfarin overdosage. The second mortality was in a patient with MPS with essential thrombocytosis. This patient developed pancytopenia 6 months after transplant which was complicated by Hemophagocytic Lymphohistiocytosis(HLH),

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renal failure, and disseminated fungal sepsis. The third patient died 25 months after transplant due to the recurrence of IVC leiomyosarcoma which was unresponsive to treatment. All four pediatric recipients were well at follow-up.

Univariate analysis identified MELD score at transplantation and pre-operative AKI as risk factors for overall survival in the adult BCS cohort. Multivariate analysis confirmed pre-operative acute kidney injury as the only independent predictor of overall survival (p=0.013; Table – 3)

3.4 Comparison with Overall Adult Non-BCS LDLT Patients:

Significant differences in key patient characteristics were identified between the adult BCS cohort and the overall adult non-BCS LDLT recipients (data not shown). In comparison to non-BCS recipients, BCS recipients were significantly younger (35±9.8 vs 49.9±11.7, p<0.001), more likely to be female (40% vs 21.7%;p=0.053), have lower Charleston comorbidity index (median 1 vs 3;p<0.001) and received grafts with higher GRWR (1.16±0.27 vs 0.97±0.28;p=0.004).

3.5 Comparison with PSM Matched Non-BCS Cohort (Table – 4)

Using propensity score matching 19 adult BCS recipients were matched with 50 non-BCS adult LDLT recipients as described in the methods section. One patient, a 30-year-old lady with Essential thrombocytosis who underwent LDLT was not matched and was removed from the comparative analysis. She had a smooth postoperative course but developed complications of HLH, bone marrow suppression, and fungal sepsis, 6 months after the transplant, and died. Demographic, pre-operative, intraoperative, and postoperative parameters in the BCS and non-BCS groups are compared in Table.4. As expected, both groups were well matched for age, gender, MELD score, donor age, and gender, and GRWR. Ascites at presentation (p<.001) and co-existing

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PVT (p=0.022), but not high-grade PVT (p=0.061), were significantly different between the two groups.

BCS patients undergoing LDLT had longer cold ischemia time(p=0.015), greater blood loss(p=0.005), and needed more red cell transfusion(p=0.043). There was no difference in major morbidity, the need for early re-operation, duration of ICU stay, need for ICU and hospital readmissions, and 90-day mortality. The BCS cohort however had increased hospital stay (p=0.037) and higher late venous outflow complications(p=0.018). One-year and 3-year survival of the BCS and matched non-BCS cohorts were 84.2% vs 94% and 70% vs 91.9%, respectively (log-rank, p= 0.09,Figure 4B).

4. DISCUSSION:

Budd-Chiari syndrome is an uncommon disorder characterized by hepatic venous outflow obstruction leading to hepatic venous congestion and liver failure. Prothrombotic conditions are a frequent cause of primary BCS in the West whereas idiopathic membranous obstruction of vena cava(MOVC) or Inferior vena cava(IVC) thrombosis are reportedly more common in the east.[18] The clinical presentation of BCS depends on the rapidity and severity of venous occlusion. BCS may be completely asymptomatic and diagnosed incidentally in up to 15% of patients.[19] Untreated acute or fulminant BCS is associated with a mortality risk of up to 60%.[20]

A range of treatment options is available for BCS ranging from long-term anticoagulation through radiological interventions to shunt surgery and liver transplantation. All these treatments aim to correct the mechanical obstruction and improve liver function, though the underlying cause for BCS remains untreated. LT is usually indicated when other options are not appropriate or failed. The Rotterdam score was developed to assess the need for liver transplantation in BCS.[21]

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A score of greater than 1.5(Class 3) predicts high 3-month mortality, needing LT. In our series, only 9 patients had a score greater than 1.5. However, the Rotterdam score does not consider other indications for LT in these patients such as HCC and HPS. Many of these patients have had failed interventions and need regular large volume paracentesis predisposing them to malnutrition, renal impairment, and infections. Unresectable retro-hepatic caval tumors (leiomyosarcoma) involving all the three major hepatic veins can cause secondary BCS like picture with liver cell failure. In such patients, liver transplantation may be the only real therapeutic option in the absence of disseminated disease especially if they are young.[22]

DDLT is an established treatment for BCS with good short-term and long-term outcomes reported by several studies and registry databases.[23,24] The LDLT experience is limited consisting mainly of single centre series (Table-5). While several of these reports have discussed the technical challenges of performing LDLT in BCS, there is no study comparing outcomes of LDLT for BCS with LDLT for other indications. We have shown in our study that the BCS cohort is dissimilar to the standard LDLT recipient profile. Associated comorbidities such as cardiovascular disease which are responsible for a significant proportion of early and late mortality after LT are uncommon in BCS patients. Hence, any comparison of outcomes should only be performed after adjusting for these confounding factors. We have therefore used PSM to identify a matched adult LDLT cohort for comparison. We show that BCS patients are more likely to have associated high-grade PVT, longer cold ischemia time, more intraoperative blood loss, and increased long-term morbidity in the form of venous outflow complications. Early and long-term survival was similar. Pre-operative AKI was identified as the only predictor of overall survival in our BCS cohort. Mentha et al also reported AKI as a risk factor in patients with BCS undergoing DDLT.[24]

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Optimal hepatic venous outflow reconstruction is the key to successful transplantation for BCS where outflow obstruction can occur at multiple levels. DDLT has the advantage of using the retro-hepatic IVC of the retrieved graft for re-establishing venous outflow which simplifies the procedure. In the LDLT setting, the approach to venous reconstruction has to be tailored to pre-operative imaging and intra-operative findings. While preserving the retro-hepatic cava does simplify the LDLT procedure, any caval webs or stenosis should be dealt with to ensure good graft venous outflow. Venous outflow reconstruction has been the main source of late morbidity in our series including one early mortality. Two patients who developed late outflow complications had undergone neo-cava reconstruction with conjoined iliac veins. Fibrotic structuring of the anastomotic suture lines in combination with the prothrombotic tendency could have contributed to these stenoses. Yoon et al reported on the use of a synthetic graft for caval reconstruction in their series of 5 patients needing caval replacement in BCS. They reported excellent long-term outcomes though one patient was found to have a redundant folded graft on surveillance CT.[25] It is possible that the use of stiffer graft material such as a deceased donor aorta or a synthetic graft may improve the long-term patency of the neo-cava.

We believe that long-term anticoagulation and regular screening for late outflow complications is necessary for all patients with BCS after LDLT. BCS recipients need more frequent imaging in the post-transplant period to help identify early asymptomatic hepatic venous outflow narrowing when it is better suited for percutaneous management. We use Ultrasound Doppler specifically looking at phasicity and waveforms in the hepatic veins and the neo-cava. Our protocol is to continue patients on LMW heparin until discharge and then convert to long-term coumarin based oral anticoagulation. In situations where patients are on remote follow-up, this can be a problem due to issues with compliance and drug interactions. In our series, we had

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one late mortality (after 13 months) due to warfarin overdose-related intracranial bleed, while another patient developed graft RHV thrombosis due to non-compliance with oral anti-coagulation. This is a serious issue and can only be corrected by continuous education of the patient and regular interactions with the local clinical team. The role of dabigatran and its congeners in the long-term anticoagulation of these patients needs further study as it will avoid the need for regular monitoring necessary with coumarin derivatives.

LDLT for BCS is associated with significant morbidity & increased mortality in the published single centre series (Table -5). According to the recent Japanese LDLT registry, the 1-year, 3 year and 5-year survival rates for BCS patients were 89%, 84%, and 81%.[26] The early deaths in our series were related to the frail preoperative condition caused by repeated paracentesis and AKI compounded by the technical complexity of the surgery. One of these patients had porto-mesenteric thrombosis which is a recognized factor for worse LDLT outcomes.[27] Given the younger age of these recipients, the usual causes of delayed mortality such as cardiovascular and cerebrovascular mortality are less likely. Late deaths in this group of patients are primarily due to underlying disease processes such as MPD or the prothrombotic tendency or its treatment.

The main drawback of this study is its retrospective nature and is a report from a single large volume LDLT centre. PSM techniques would not be able to match for all possible confounding factors but are the closest approximation to a randomized trial. Despite these limitations, this is one of the larger studies reporting detailed outcomes of LDLT for BCS and to our knowledge, the only published report which compares the early and medium-term outcomes after LDLT with a well-matched control cohort.

In conclusion, we present one of the largest to-date single centre experience of LDLT for BCS. Thereby, highlighting its short and long-term outcomes, allowing for an objective

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comparison of data. LDLT is an excellent option for patients with symptomatic BCS who have failed other non-transplant options. With the BCS cohort possessing distinct pre-LT characteristics, the mortality in these patients is related to their underlying condition. Nonetheless, as shown by us, an algorithmic approach in the management of BCS makes outcomes of LDLT for BCS comparable to those for other indications.

Figure Legends:

Figure 1. Algorithm for liver transplantation in BCS

Figure 2. LDLT for BCS: A – Thinned out cava due to prior IVC stenting; B – Neocava reconstruction using deceased donor preserved IVC; C – Right hepatic vein web; D – After implantation, anterior sector (both v5 and v8) reconstruction using deceased donor preserved iliac vein to the neocava

Figure 3. Histogram and Jitter Plots of propensity scores of BCS and non-BCS cohorts before and after matching

Figure 4. Kaplan-Meier survival analysis

A. 1-year and 3-year survival estimate of overall BCS cohort

B. Overall survival of BCS Adult LDLT patients and PSM non-BCS LDLT patients (Log-rank test, p=0.09)

 doi:10.20944/preprints202110.0012.v1

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TABLE 1: Demographics of LDLT-BCS patients

Patient characteristics	N = 24
Age in years (Median)	
Adult (n =20)	34.5(28,40)
Children (n =4)	2 (1,5.25)
Gender - Male	15 (62.5%)
Etiology:	
Primary BCS	22(91.7%)
Myeloproliferative diseases – JAK 2 Mutation	3
Anti-phospholipid antibody syndrome (APLA)	3
Protein C and S, AT 3 deficiency	2
IVC web	2
Idiopathic	12
Secondary BCS	2(8.3%)
Leiomyosarcoma of inferior vena cava	2
Presentation	
Sub-acute	3(12.5%)
Chronic	21(87.5%)
Clinical presentation:	
Ascites	24(100%)
Jaundice	15(62.5%)
Hepatic encephalopathy	7(29.2%)
Spontaneous Bacterial Peritonitis (SBP)	5(20.8%)
Blood Stream infection (BSI)	5(20.8%)
AKI	5(20.8%)
Site of hepatic venous outflow block	
Hepatic veins (HV) alone	16(66.7%)
Inferior vena cava (IVC) alone	3(12.5%)
Combined obstruction	5(20.8%)
Child's Score	
Child B	3(12.5%)
Child C	21(87.5%)
MELD score at transplant (Median)	16(12,20)
Rotterdam score (Median)	1.1(1.05,2.31)
Class I	13(54.2%)
Class II	2(8.3%)
Class III	9(37.5%)
Prior radiological vascular interventions	6(25%)
Angioplasty / Stenting	6
Shunt Surgery	1
Concomitant portal vein thrombosis	6(25%)
Yerdel's Type 2	3
Yerdel's Type 3	1
Yerdel's Type 4	2
Indication for transplant	
Progressive liver dysfunction	4(16.6%)
Ascites needing frequent LVP/SBP	11(45.9%)
Failed percutaneous interventions	6(25%)
Hepatocellular carcinoma	2(8.3%)
Severe HPS	2(8.3%)
Unresectable caval tumor	2(8.3%)

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TABLE 2: Intraoperative and postoperative details of LDLT-BCS patients

Parameters	N = 24
Graft	
Right lobe	18(75%)
Left lobe (2 adults & 1 child)	3(12.5%)
Left lateral segment (all children)	3(12.5%)
Outflow Reconstruction	
Inferior Vena cava (IVC) replacement	7(29.1%)
Inferior Vena cava (IVC) preserved (adults & children)	16(66.7%)
Repair/ plasty of native cava	3
LHV-atrial anastomosis	1(4.2%)
Portal vein thrombosis Management (n=6)	
Eversion thrombectomy	3(50%)
Reno-portal Inflow	2(33.3%)
Mesenterico-portal Jump graft	1(16.7%)
Biliary reconstruction	
Adults	
Duct to Duct	15(75%)
Roux Y Hepaticojejunostomy	5(25%)
Children	
Duct to Duct	1(25%)
Roux Y Hepaticojejunostomy	3(75%)
Postoperative morbidity	
Early HVOT	1(4.2%)
Bleeding	1(4.2%)
Early biliary complications	3(12.5%)
Bloodstream infections (BSI)	8(33.3%)
Acute kidney injury	7(29.2%)
Prolonged ascitic drainage	1(4.2%)
Chyle leak	3(12.5%)
Reoperation	2 (8.3%)
Major morbidity (Clavien-Dindo Grade 3b/4)	5(20.8%)
90-day Mortality	3(12.5%)
Median ICU stay (in days)	5(4,12)
Median hospital stays (in days)	19.5(17,28)
Median follow-up(months)	23(11,40)
Late biliary strictures	3(12.5%)
Late Hepatic venous outflow complications	3(12.5%)
Survival - 1-year survival	83.3%
3-year survival	71%

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TABLE 3: Univariate and Multivariate analysis of risk factors for mortality in adult BCS recipients

Parameters	Survivors (14)	Died (6)	Univariate analysis	Cox Multivariate analysis		
			P-value	P-value	Exp (B)	95% CI
Age	35.7(±9.7)	34.2(±10)	0.749			
Male gender	8(57%)	4(66.7%)	1.000			
BMI	25.3(±4.4)	23.5(±5.6)	0.473			
MELD	14.5(±3.6)	18.3(±3.3)	**0.039**	0.097	1.29	0.96, 1.73
Procoagulant tendency	7(50%)	1(16.6%)	0.325			
Pre-operative SBP	3(21%)	2(33%)	0.613			
Pre-operative AKI	1(7.1%)	4(66.7%)	**0.014**	**0.013**	11.05	1.64, 74.35
Pre-operative BSI	2(14.2%)	2(33.3%)	0.549			
Pre-operative PVT	4(28.5%)	2(33.3%)	1.000			
Neocaval reconstruction	6(42.85%)	1(16.7%)	0.354			
Donor Age	32(±6.9)	35(±7.6)	0.400			
GRWR	1.16(±0.24)	1.14(±0.16)	0.872			
Mean Cold ischemia time(min)	128(±42)	178(±150)	0.252			
Mean duration of surgery(min)	627(±129)	636(±167)	0.893			
Mean Intra-operative blood loss	1993(±1109)	2550(±1787)	0.403			
Mean Intra-operative packed RBC transfusion	5.2(±4.1)	8.5(±7.6)	0.220			

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TABLE 4: Comparison of BCS adult LDLT patients and PSM non-BCS LDLT patients

Pre-operative factors	Cases (n = 19)	Controls (n = 50)	P value
Mean Age (years)	35.5(± 9.8)	36.8(± 10.8)	0.632
Gender (Male)	12(63.2%)	35(70%)	0.579
Weight Kgs	66.1(±11.9)	62.3(±12.3)	0.251
Mean BMI	24.8(±4.6)	23.1(±4.3)	0.149
Mean MELD	15.7(± 4)	15.9(± 5.2)	0.925
Ascites	19(100%)	24(48%)	**<0.001**
Hepatic encephalopathy	5(27.8%)	11(30.6%)	0.83
Pre-operative AKI	5(26.3%)	6(12%)	0.161
PVT	6(31.6%)	4(8%)	**0.022**
High grade PVT	3(15.8%)	1(2%)	0.061
Donor and graft factors			
Age	33.4(±6.9)	33.2(±9.5)	0.617
Gender (Male %)	12(63.2%)	23(46%)	0.282
Graft weight	755(±188)	685(±146)	0.105
Mean GRWR	1.15(±0.28)	1.12(±0.21)	0.591
Graft type (right lobe)	17(89.5%)	47(94%)	0.611
Intra-operative factors			
Mean Cold ischemia time CIT (min)	145(±90)	96(±63)	**0.015**
Mean Intraoperative Blood loss(ml)	2195(±1350)	1169(± 738)	**0.005**
Mean Packed RBC transfusion	6.24(±5.4)	3.95(±3.8)	**0.043**
Total blood products transfusion	14.4(±14.1)	7.8(±8.9)	0.023
Mean Duration of surgery (min)	639(±135)	600(±129)	0.276
Post-operative morbidity & outcomes			
AKI	8(42.1%)	7(14.3%)	**0.022**
BSI	8(42.1%)	7(14.3%)	0.058
Bleeding	2(10.6%)	4(8%)	1.000
Early graft dysfunction	5(2.63%)	7(14.3%)	0.294
Early vascular complications	0	1(2%)	1.000
Early outflow complications	1(5.3%)	0	0.275
Early biliary complications	3(15.8%)	2(4%)	0.124
Chyle leak	2(10.5%)	2(4%)	0.303
Prolonged ascitic drainage	1(5.3%)	3(6%)	1.000
Reoperation within 90 days	2(10.5%)	4(8%)	0.664
Acute cellular rejection	4(20%)	10(25%)	0.756
Median ICU stay(days)	5(4,9)	5(4,6)	0.416
ICU readmission	4(21.1%)	7(14%)	0.480
Median Hospital stay(days)	20(16,28)	16(14,21)	**0.037**

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Major morbidity (Clavien-Dindo grades 3b/4)	3(15.8%)	48(16%)	1.000
90-day mortality	3(15.8%)	2(4%)	0.124
Late outflow complications	3(15.8 %)	0	**0.018**
Readmission within 6 months	9(47.5%)	18(36%)	0.419
Overall survival	14(73.7%)	46(92%)	0.102

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TABLE – 5: STUDIES PUBLISHED ON LDLT FOR BCS

SERIES	(N)	Morbidity (%)	Mortality (%)	Mean follow-up (Months)	Recurrence (%)	1-year survival (%)	3-year Survival (%)
Our study (2020)	24	37.5	12.5	28.6	12.5	83.3	71
Young-In yoon et al (2019)[25]	5	-	Nil	126	Nil	100	100
Fatih Gonultas et al [#] (2019)[28]	17	35.2	Nil	-	-	-	-
Umeshita et al [@] (2019)[26]	57	-	-	-	-	89.5	83.7
C. Karaca et al (2017)[10]	22	31.8	18.2	43	-	-	-
Pahari H et al (2016)[29]	9	44.4	11.1	15.7	-	-	-
Cengiz Ara et al (2016)[9]	39	48.7	33.3	16.1	5.1	-	-
Dogrul AB et al [#] (2015)[30]	10	-	20	10.5	7.1	-	-
Bas et al (2012)[31]	3	33.3	Nil	18	-	-	-
G.S Choi et al (2010)[32]	4	-	Nil	19.5	-	-	-
Yamada T et al (2006)[33]	9	-	11.1	-	40	-	-

[#] - Only BCS LDLT patients were included; [@] - Registry by the Japanese liver transplantation society

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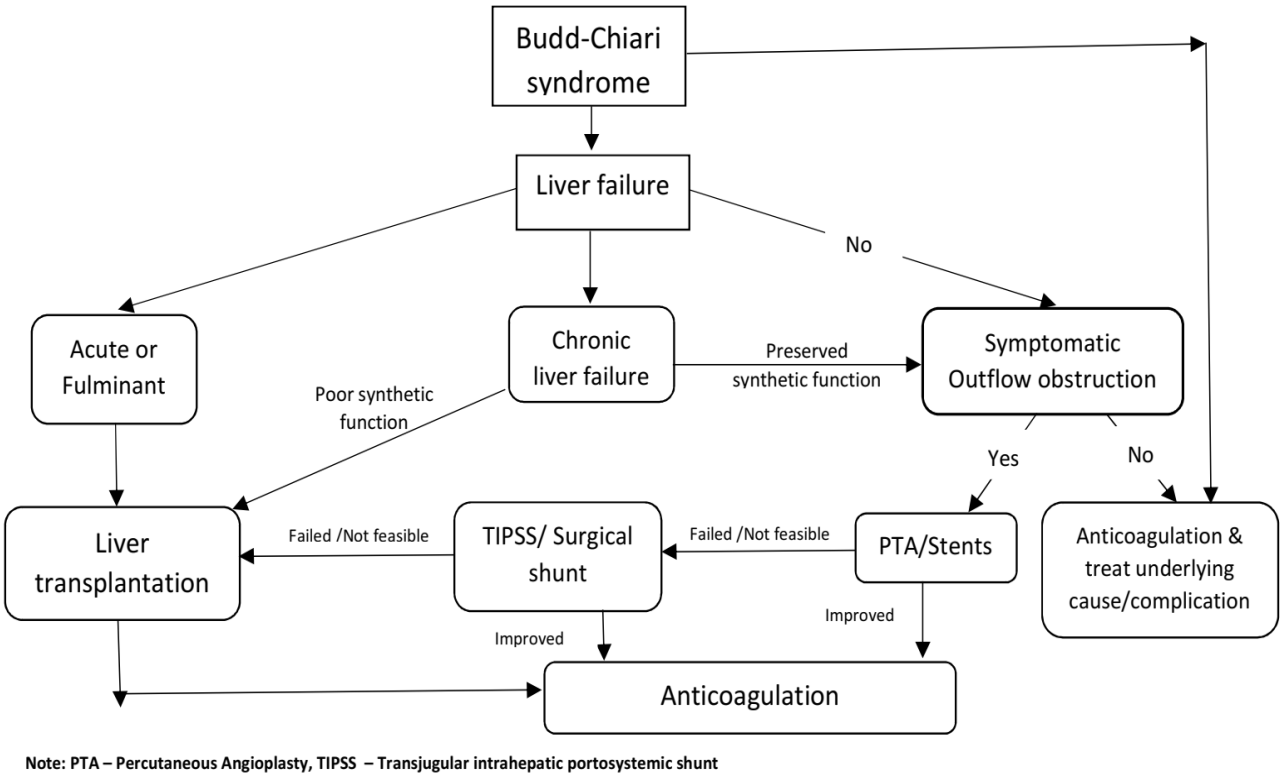

Figure 1. Algorithm for liver transplantation in BCS

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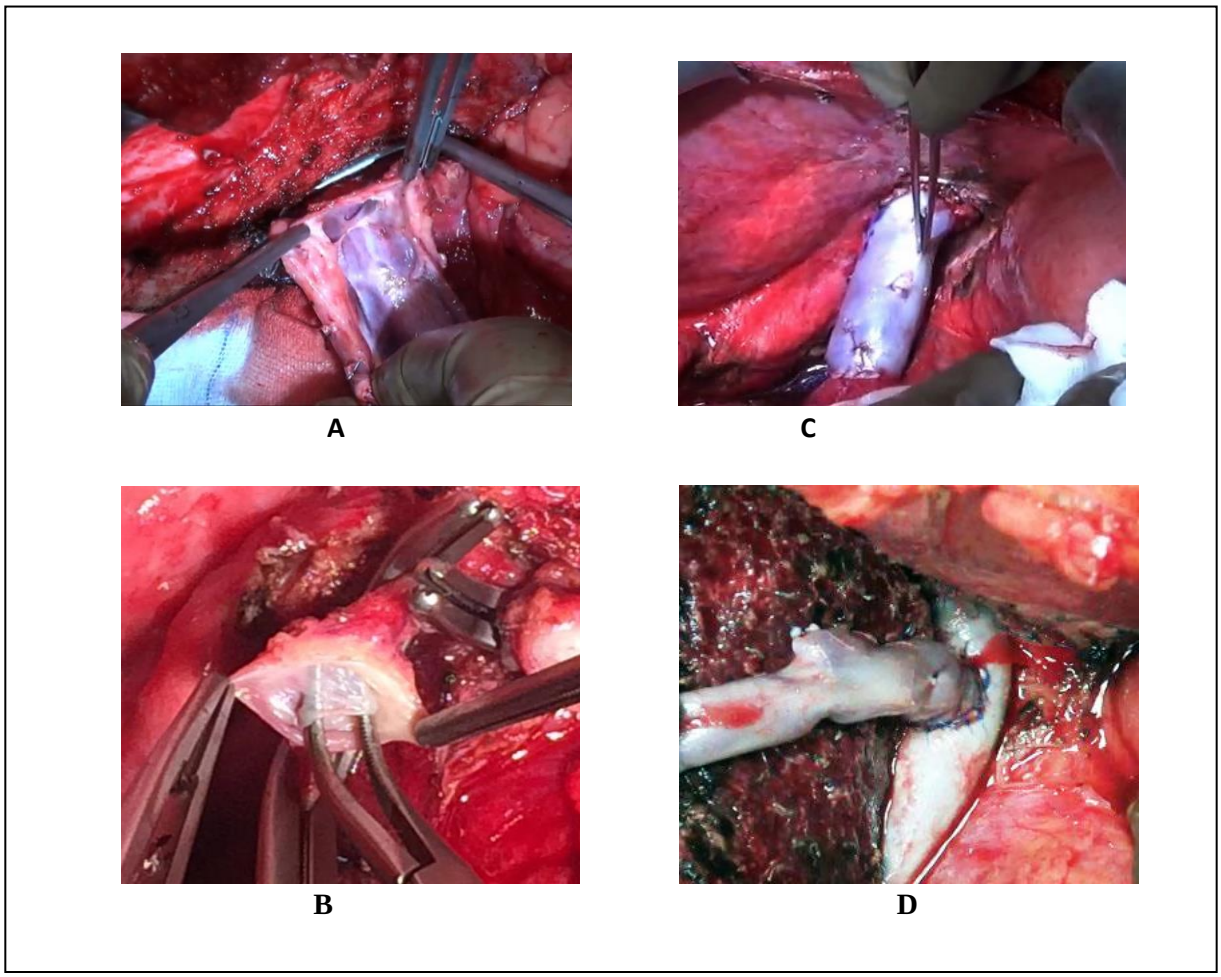

Figure 2. LDLT for BCS: A – Thinned out cava due to prior IVC stenting; B – Neocava reconstruction using deceased donor preserved IVC; C – Right hepatic vein web; D – After implantation, anterior sector (both v5 and v8) reconstruction using deceased donor preserved iliac vein to the neocava

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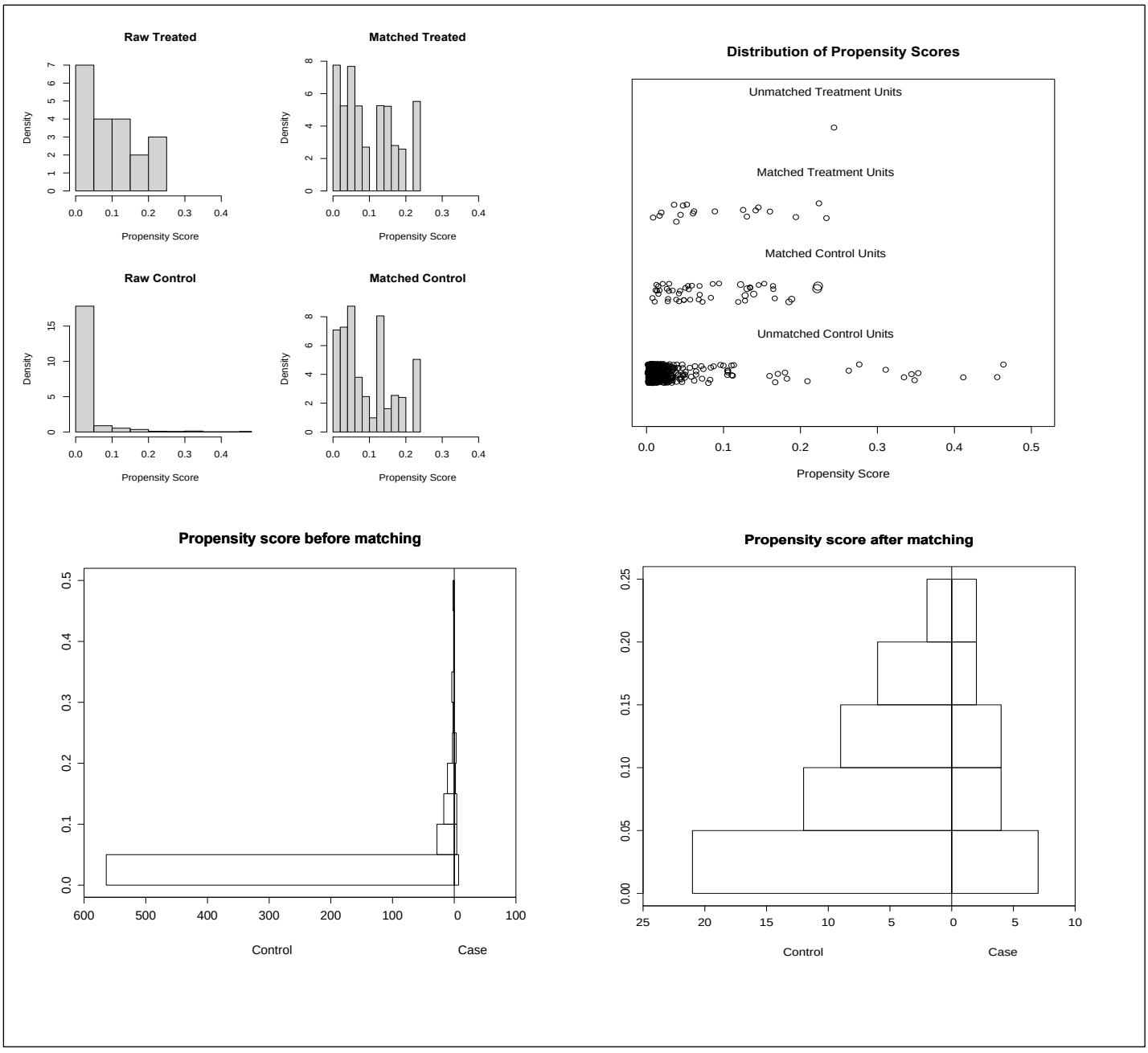
Figure 3. Histogram and Jitter Plots of propensity scores of BCS and non-BCS cohorts before and after matching



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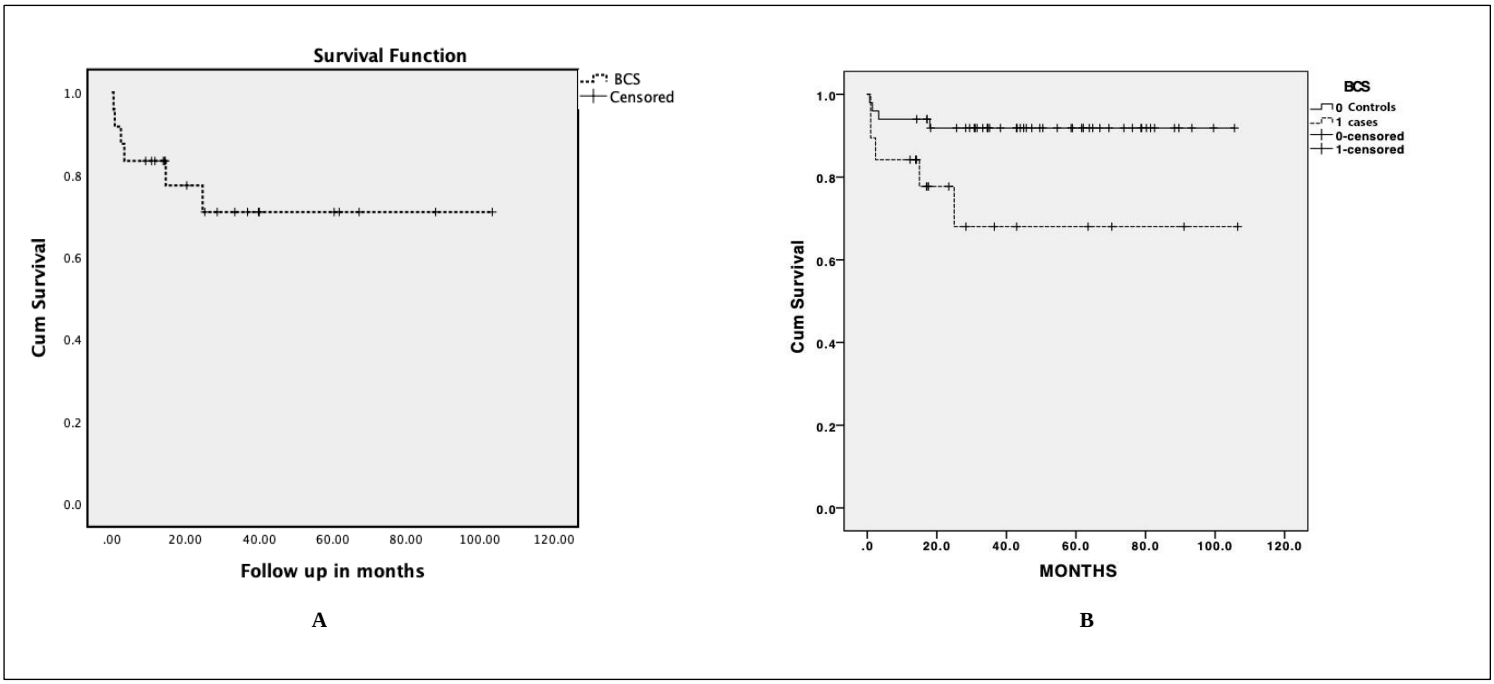

Figure 4. Kaplan-Meier survival analysis

A. 1-year and 3-year survival estimate of overall BCS cohort

B. Overall survival of BCS Adult LDLT patients and PSM non-BCS LDLT patients (Log-rank test, p=0.09)