

# Combined off Pump Coronary Artery Bypass Graft and Liver Transplant

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## ABSTRACT

**Background:** Prospective recipients of liver transplant (LT) have a high prevalence rate of coronary artery disease (CAD) requiring revascularization. In patients of Child Turcot Pugh Class B and C performing LT prior to cardiac revascularization on cardiopulmonary bypass leads to a high risk of major adverse cardiovascular events (MACE). Whereas, isolated cardiac surgery prior to LT has perioperative risk of coagulopathy, sepsis, and hepatic decompensation. We present four cases of end stage liver disease who underwent concomitant living donor liver transplant (LDLT) with off pump coronary artery bypass graft (OPCAB) in an effort to decrease the morbidity and mortality.

**Methods:** The cases were performed in a tertiary care centre over two years. Four patients scheduled for LDLT, who were diagnosed with significant CAD, underwent single sitting OPCAB and LDLT. Cardiac surgery was performed first and once patient was stable, it was followed by LDLT. The morbidity parameters in terms of duration of intubation, blood transfusion, hospital stay, ICU stay, requirement of dialysis, atrial fibrillation and sepsis was compared with similar studies.

**Results:** The blood transfusion requirement (median 8 units PRBC), incidence of atrial fibrillation (25%), sepsis (25%), and renal dysfunction (0%) was less than the combined surgery conducted on cardiopulmonary bypass. The rate of median intubation time, length of ICU stay, hospital stay, and one year mortality rate was comparable with other studies.

**Conclusions:** Morbidity with combined OPCAB and LDLT is less than combined on pump coronary artery bypass surgery with LDLT. Combined CABG with LDLT may be performed with acceptable outcomes in CTP class B and C cirrhosis.

**Keywords:** *Living donor liver transplant, liver transplant, off pump coronary artery bypass graft, coronary artery bypass graft, combined surgery, CABG*

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**Submitted:** 22-Dec-2019 **Revised:** 25-Mar-2020 **Accepted:** 30-May-2020 **Published:** 19-Apr-2021

Liver transplant (LT) in patients with end stage liver disease (ESLD) is the second most common transplant conducted every year,<sup>[1]</sup> constituting 22% of all organ transplants. Non-hepatic causes of mortality in LT patients are attributed to infection, neurologic and cardiac adverse events, where the incidence of the latter remains high.<sup>[2,3]</sup> Late events and deaths (odd ratios of 3.07 and 2.56, respectively) after 3 years are not less either.<sup>[4]</sup> Potential

LT recipients have a high prevalence rate for coexisting coronary artery disease (CAD), and recent data shows that if appropriately revascularized, severity or extent of CAD does not impact post LT survival.<sup>[5]</sup> There is a reluctance however to perform LT prior to cardiac revascularization due to the perioperative risk associated with CAD. In patients with ESLD of Child Turcot Pugh (CTP) Class B

Access this article online	
Quick Response Code:	Website: www.annals.in
	DOI: 10.4103/aca.ACA_194_19

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**How to cite this article:** Juneja R, Kumar A, Ranjan R, Hemantlal PM, Mehta Y, Wasir H, *et al.* Combined off pump coronary artery bypass graft and liver transplant. *Ann Card Anaesth* 2021;24:197-202.

and C, there remains a high risk of morbidity and mortality due to coagulopathy, sepsis, and hepatic decompensation.<sup>16]</sup> To improve outcomes in this subset of patients, combined single sitting conventional coronary artery bypass graft surgery (CCAB) on cardiopulmonary bypass (CPB) and orthotopic liver transplant (OLT), [CCAB-OLT] has been performed with acceptable morbidity and mortality.<sup>17,8]</sup> We present four cases of ESLD who underwent concomitant living donor liver transplant (LDLT) with off pump coronary artery bypass graft (OPCAB). To the best of our knowledge, this is the first case series of concomitant OPCAB and LDLT.

Four patients of ESLD of different etiology [Table 1], having a mean age of 60 years scheduled for LT, was observed prospectively. Three had model for end stage liver disease (MELD) score >15 and CTP Class C. All had normal left ventricular ejection fraction (LVEF) [Table 1] and underwent stress thallium and coronary calcium score (CCS). Invasive coronary artery angiography was performed in all four cases as CCS was more than 100 in all patients. Two patients had severe triple vessel disease, one had double and the fourth had single vessel disease. Considering severe CAD in three patients with CTP class C and stent stenosis in the fourth with CTP class A, the heart team opted for concomitant OPCAB & LDLT in three cases of CTP class C with high SYNTAX<sup>9]</sup> score and fourth case with CTP Class A and recurrent stent thrombosis.

#### **ANAESTHESIA MANAGEMENT AND MONITORING**

Cardiac surgery was performed first and managed by cardiac anesthesiologists. After completion of the cardiac surgical procedure, LT anesthesiologists managed the LT. Beta blocker and Terlipressin were stopped 72 h prior to surgery in patients taking these medications. Antibiotics were started a day prior to surgery as per the institute protocol. Antibiotics were Piperacillin-Tazobactam 4.5 g iv tds, Teicoplanin 400 mg iv bd, Fluconazole 200 mg iv od, and Methyl prednisolone 10 mg/kg. Piperacillin-Tazobactam 4.5 g iv was repeated every 6 h intraoperatively. Pantoprazole 40 mg was administered orally on the morning of surgery; benzodiazepine was omitted as premedication. Apart from standard ASA monitoring, urine output, oropharyngeal temperature, invasive arterial pressure, pulmonary artery pressures, cardiac output, and calculated variables were monitored. Forced air warmer was used, and a warming mattress was placed beneath the patient. Fluid warmer was also used to transfuse warm intravenous fluid. Due to long duration of surgery, all pressure points were adequately

padded. In addition to a 7 Fr triple lumen central line, a 9 Fr sheath with pulmonary artery catheter was also inserted in the right internal jugular vein. Anesthesia was induced with thiopentone 2.5 mg/kg body weight, fentanyl citrate 2 microgram/kg, and endotracheal intubation was facilitated by vecuronium bromide 0.1 mg/kg. Anesthesia was maintained with isoflurane, fentanyl infusion at 0.5 to 1.0 microgram/kg/Hr, and atracurium at 0.5 mg/kg/Hr. Intraoperatively plasmalyte and 5% albumin was used as crystalloid and colloid, respectively. Left internal mammary artery and saphenous veins were used as conduits for coronary revascularization after midline sternotomy. Graded doses of heparin 100-150 IU/Kg were used to achieve activated clotting time (ACT) of >300 seconds. Heparin was neutralized with protamine sulphate (1 to 1.3 mg/Kg) to reduce ACT to <150 s after completion of OPCAB. A goal to maintain cardiac index  $\geq 2.0$  l/m<sup>2</sup> was attempted.

After completion of OPCAB, we waited for some time for the patient to be hemodynamically stable and decrease in volume of chest drain. Three patients required re-exploration due to excessive chest tube drainage in the first hour following OPCAB.

Classical Mercedes Benz incision was given in the subcostal region in all cases for LDLT. Related donor liver was being harvested in the adjacent operating room simultaneously. One unit of single donor platelet concentrate was transfused before initiating dissection of diseased liver. All blood and blood products were transfused preferably before the completion of dissection of diseased liver based on findings of thromboelastograph. Inj. Methyl prednisone 10 mg/kg was administered just prior to transplanting the harvested liver. Transesophageal echocardiography was used perioperatively to monitor hemodynamics not only in cardiac surgery but also in LT [Figure 1]. A cavo-caval anastomosis was constructed using full clamp, followed by portal anastomosis. This was followed by hepatic artery and bile duct anastomosis. A good bleed out was done before anastomosis of the portal vein. Tacrolimus, mycophenolate mofetil, and steroids were the immunosuppressant used in all patients. All of the recipients remained hemodynamically stable during reperfusion. Platelet concentrates and fresh frozen plasma were avoided after the completion of portal anastomosis to decrease the risk of graft thrombosis. However, packed red blood cell (PRBCs) were transfused to correct decreased hemoglobin level. Median of 8 units of packed cells, 6 units of fresh frozen plasma, and 2 units of platelets were transfused intraoperatively. Median duration of anesthesia was 1200 min.

Continuous infusion of IV fentanyl 0.5  $\mu$ gm/kg and IV atracurium 0.25 mg/kg was maintained in postoperative ICU

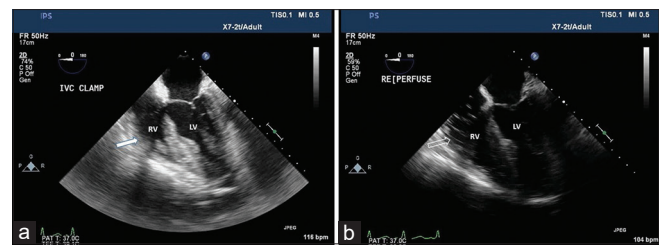
**Table 1: Demographic characteristics and clinical profile of liver transplant recipients**

Variables	Case 1	Case 2	Case 3	Case 4
<b>Patient Characteristics</b>				
Age (years)	57	56	51	67
BMI (kg/m <sup>2</sup> )	24	26	26	33
Diagnosis	Chronic liver disease	Cryptogenic liver disease	Alcoholic cirrhosis	Cryptogenic liver disease
Hypertension	6 yrs	-	-	8 yrs
CTP score	10	10	10	6
CTP class	C	C	C	A
MELD	18	20	19	7 (Tumor MELD-22)
<b>Laboratory values</b>				
Hb (mg/dl)	9.5	10.4	8	12.6
PT (secs)	12	17	20	11
aPTT (secs)	28	43	44	26
INR	1.9	1.66	1.8	1.09
<b>Clinical parameters</b>				
Jaundice	-	+	+	+
Portal hypertension	+	+	+	-
Ascites	+	+	+	-
Bilirubin (mg/dl)	3.8	7.5	6.2	1.5
Albumin (mg/dl)	2.4	2.5	2.0	4.4
<b>Investigation</b>				
LVEF	>60%	>60%	>55%	>60%
Stress thallium	-	+	+	+
Calcium score (Agastaton units)	285	1787	2192	718
CCTA	Not done	Not done	Not done	not done
Invasive Coronary Angiography	+	+	+	+
No. of coronary arteries involved	3	2	3	1
OPCAB	+	+	+	+
<b>Intraoperative transfusion</b>				
Units of PRBC	10	9	14	2
Units of FFP	6	6	15	-
Units of SDAP	4	2	2	-
Units of 100 ml 20% albumin transfused	0	0	0	2
Chest drain Removal (day)	16	4	6	2
<b>Postoperative</b>				
Abdominal Drain (days)	17	14	10	3
ICU Stay (days)	6	16	5	8
Hospital stay (days)	21	20	14	21
Units of PRBC transfused	4	4	3	0

BMI=Body mass index, CTP=Child Turcot Pugh, MELD=Model for end stage liver disease, PT=Prothrombin time, aPTT=Activated partial thromboplastin time, INR=International normalized ratio, SDAP=Single donor aphaeretic platelets, LVEF=Left ventricular ejection fraction, CTA=Coronary computed tomography angiography, FFP=Fresh frozen plasma, PRBC=Packed red blood cells

for next 10-12 h. However, pain is less in recipients due to high-dose corticosteroids and resection of all nerves around the diseased liver. Ecospirin 150 mg was started when platelet count was >40,000, INR <1.7 and drain color was serous and low-molecular-weight heparin 0.6 mg bd was added subsequently for the first 2 weeks. Clear liquid feed through Ryle's tube was started in all patients on the day after extubation. Patients were shifted to high dependency unit after a week.

Median duration of postoperative mechanical ventilation was 2 days, median ICU stay was 7 days, and median hospital stay was 20 days. Morbidity such as sepsis, acute lung injury, atrial fibrillation, and pleural effusion was seen in 25% of the cases [Table 2]. None of the patients developed renal failure or required renal replacement therapy (RRT). Patients were followed up for 2 years. There was one mortality at the end of the first year.



**Figure 1:** (a) Mid esophageal 4-Chamber view depicting empty right ventricle (solid arrow) and left ventricle during clamped inferior vena cava in the anhepatic phase. (b) Mid esophageal 4-Chamber view depicting filled right ventricle (hollow arrow) with micro air bubbles in right atrium, and left ventricle during reperfusion after declamping the inferior vena cava

## DISCUSSION

Improved surgical outcomes have led to LT being performed in older patients who have a 16.2% incidence of severe CAD requiring revascularization.<sup>[10]</sup> Of these,

**Table 2: Comparison of outcomes of OPCAB/LDLT with CABG/OLT**

Parameter	Case Series (n=4)	Axelrod <sup>[7]</sup> (n=5)	De Stephano <sup>[8]</sup> (n=5)
Cardiac surgery, min	342 (300-386)	99 (68-125)	233 (210-276)
LT surgery, min	620 (510-600)	-	362 (351-380)
Anesthesia, min	1200 (960-1320)	834 (705-932)	769 (705-836)
Intubation, d (median)	2 [1-5]	-	2 [1-3]
ICU LOS, d (median)	8 [5-16]	10 [2-40]	5.5 [3-8]
Hospital LOS, d (median)	20 [14-21]	21 [07-59]	13 [11-14]
CTP Class C (No. of pts)	3	4	3
MELD Score	18 [7-20]	Not Done	17 [11-18]
Deaths (<1 yr)	1	1	1
Atrial Fibrillation (%)	25	-	40
Sepsis (%)	25	-	66
Intraoperative PRBC Transfusions (median)	8	-	12

OLT=Orthotopic liver transplant LOS=Length of stay, CTP=Child Turcot Pugh, PRBC=Packed red blood cells

13.2% remain asymptomatic, warranting additional cardiac evaluation in recipients of LT.

Stress thallium is the first line modality of CV risk assessment for LT recipients.<sup>[11]</sup> In addition, CCS has been incorporated by computed tomography (CT) in all patients undergoing LT with  $\geq 2$  risk factors, which include age >40 yrs, diabetes mellitus, prior cardiovascular disease, h/o smoking, hypertension, dyslipidaemia, stroke, history of revascularization, left bundle branch block, and arrhythmia.

Patients having CCS <100 and a negative stress thallium underwent only coronary CT angiography (CCTA).<sup>[12]</sup> Patients having any of the following four factors, which include CCS >100, stress thallium positive, high risk of CAD and history of previous CABG are subjected to invasive coronary angiography (CAG). All patients are not subjected to CCTA and CAG both, due to the risk of developing contrast induced nephropathy except one patient who was operated long ago when the CCS was not an acceptable criterion for determining the severity of CAD [Table 1].

We compare data from our series with reports on 1) isolated cardiac surgery in cirrhotic patients and 2) combined cardiac surgery with LT (CCAB + LT).

Most centers mandate treatment of cardiac lesions prior to LT.<sup>[6,13-15]</sup> However, cardiac surgery on CPB in cirrhotic patients, especially advanced states such as CTP class B, C, and MELD score >14 are associated with alarmingly high morbidity and mortality rates, ranging from 3 to 100%.<sup>[14,15]</sup>

Mortality following cardiac surgery in 44 cirrhotic patients was reported as 3.2, 42 and 100% in CTP class A, B, and C patients respectively.<sup>[6]</sup> A Cornell study reported 100 percent morbidity and 80% mortality in CTP class B patients.<sup>[16]</sup> Filsoufi reported major postoperative

complications in 20, 56, and 100% of patients in CTP class A, B, C respectively.<sup>[14]</sup> An overall mortality of 27% with one-year survival rates as 80, 45 and 16 percent for class A, B, and C, respectively, were observed. Hayashida reported 100% mortality in CTP class B patients when CPB was used and 50% without use of CPB in 18 patients.<sup>[17]</sup> They also reported 25-100% morbidity in CTP class A patients and deemed CTP class B and C as contraindications to the use of CPB in cardiac interventions.<sup>[18]</sup> This has led to refusal of LT and reduced options for the meaningful survival of these patients.<sup>[19,20]</sup>

Major perioperative complications in these cases occur due to poor nutritional status, coagulopathy, sepsis, renal failure, bleeding, fluid imbalance, pulmonary dysfunction, and hepatic decompensation. A decrease in hepatic blood flow during anesthesia and surgery causes further liver damage with deterioration of liver function.<sup>[13,21]</sup>

Following improvements in the management of hepatic dysfunction, anesthesia, and surgical techniques over the years, combined sequential cardiac surgery and LT has been performed in cardiac patients with ESLD who are too sick to undergo either surgery alone.<sup>[7,8,13,22]</sup> A small number of case series with few cases in each report and a few single patient case reports have been published so far observing improved prognosis.<sup>[7,22]</sup>

In 9 cases of CTP Class A and B, 5 CABG (2 asymptomatic) and 4 aortic valve replacement (AVR) had 30-day mortality of one (11%) patient and 1-year mortality of 2 (22%) patients.<sup>[7]</sup> In another study consisting of 5 CABG patients with a mean MELD score 22, there was no perioperative mortality but 1 (20%) patient died at 5 months.<sup>[8]</sup> In another study consisting of 10 cases of CTP class B and C, 2 (20%) patients died after discharge.<sup>[22]</sup> In a series consisting of 15 cases with 9 CABG, 4 AVR, and 2 combined pathology, there were 4 patients with CTP class B and 11 with C, with a mean MELD score of 24. Four (26%) deaths occurred

in the first year of surgery.<sup>[23]</sup> Mortality figures were much less than isolated cardiac surgery in cirrhotic patients.

Morbidity in these patients is described in terms of duration of intubation, hospital stay, ICU stay, requirement of dialysis, incidence of atrial fibrillation, stroke, and sepsis. Duration of intubation varied from mean duration of intubation was 3 days, ICU stay varied from 6-10 days and length of hospital stay from 19-21 days.<sup>[7,22,23]</sup> Atrial fibrillation occurred in 40-53.3% cases,<sup>[8,23]</sup> sepsis occurred in 33% cases;<sup>[8,22]</sup> renal dysfunction requiring dialysis in 26.7- 67% cases.<sup>[8,22,23]</sup> Chests were packed and left open after the cardiac surgery part in all cases, to observe for hemorrhage.<sup>[7,8,22]</sup> No sternal wound infections were observed.<sup>[7]</sup> Re-exploration was done to check for abdominal or thoracic hemorrhage in three cases.<sup>[7,8,22]</sup> On an average 30 platelets, 12 packed red cell units were transfused per case according to a study.<sup>[8]</sup> Pericardial effusion requiring re-exploration occurred in one case.<sup>[7]</sup> Stroke occurred in one case of CTP class C patients.<sup>[22]</sup> Morbidity following cardiac surgery combined with LT too was observed to be less than in isolated cardiac surgery in cirrhotic patients.

Ben Ari *et al.* reported isolated OPCAB in a patient with CTP class C cirrhosis.<sup>[13]</sup> Perioperative course was uneventful except for renal failure, which prolonged ICU stay to 10 days and hospital stay to 14 days. Lebbinck reported a case of combined OPCAB and LT in a CTP class C cirrhotic patient. They used 1.5 mg heparin, the chest was closed after OPCAB, 6 packed red cells, 16 FFP units, and 8 platelets were transfused. ICU stay was 5 days, and the patient were alive 6 months later.<sup>[24]</sup> Diaz in his review has also indicated the benefit of avoiding CPB in this subset of patients.<sup>[25]</sup>

CPB is associated with adverse outcomes due to activation of systemic inflammatory response, nonpulsatile perfusion, coagulopathy, end organ damage, haemodilution, effect on vascular permeability, and fluid balance which may be additive in cirrhotic patients [Table 3]. Avoiding CPB could theoretically improve prognosis. There is less risk of bleeding, preserved neurocognitive dysfunction, shorter time to extubation, reduced incidence of atrial fibrillation, and renal dysfunction.<sup>[13]</sup>

Considering these observations, our case series consisted of four patients, who underwent combined sequential OPCAB with live donor liver transplant (LDLT). Three cases were in CTP class C with an MELD score of 18, and one patient was in CTP class A with a MELD score of 7 (Tumor MELD Score 22). All except one were asymptomatic for CAD, which was diagnosed during preoperative evaluation. Two had triple, one had double, and the fourth

**Table 3: Risks in patients of ESLD undergoing isolated cardiac surgery**

Inherent risk in patients of ESLD undergoing isolated cardiac surgery	
a	Increased risk of hemorrhage due to coagulopathy
b	Decreased hepatic blood flow
c	Fulminant hepatic failure
d	Encephalopathy

had single vessel CAD with normal LV ejection fraction. Median intubation time, ICU, and hospital stay were 2, 7, and 20 days, respectively. These were comparable to the time periods described above for the CCAB-LT reports and isolated LT studies in CTP class C patients.<sup>[26]</sup> Thus combined cardiac surgery and LT does not lead to increased length of ICU or hospital stay [Table 2].

Blood product requirement was a median of 8 units of packed red cells, 6 units of fresh frozen plasma, and 2 units of platelets, which was less than CCAB-LT as well as isolated cardiac surgery in cirrhotic patients.

Sepsis occurred in one case (25%), which was less than CCAB-LT (33%).<sup>[8,22]</sup> Sepsis was not reported in an isolated OPCAB case in cirrhosis.<sup>[13]</sup> This supports the belief that OPCAB cases may have less risk of infection than cases conducted on CPB.

Renal dysfunction did not occur in our series, while RRT was required in 26.7-67% cases in the CCAB-LT reports.<sup>[8,22,23]</sup> There was no perioperative mortality, but one (25%) patient died within the first year, which was like the CCAB-LT reports [Table 2]. Also, these figures compare better than those for isolated cardiac surgery in patients with cirrhosis, which reported 2-100% mortality.<sup>[6,13,14,15]</sup>

Atrial fibrillation occurred in 25% of our cases while CCAB-LT series reported 33 to 53% [Table 2].<sup>[8,23]</sup> Atrial fibrillation is a common arrhythmia after CCAB though its incidence is comparatively less after OPCAB.<sup>[27]</sup> Pleural effusion after LT is a common complication and is primarily right sided. Small effusions resolve spontaneously, but if large, may require tube thoracostomy.<sup>[28]</sup> In our series, all patients had chest drains due to cardiac surgery but only one (25%) patient had drains *in situ* for a long duration. Long duration abdominal drains were required in those recipients who had pre-existing ascites [Table 1].

In this series, median duration of combined surgery, including anesthesia time, was 1200 min. Total duration (1200 min) of combined surgery consisted of anesthesia time, median duration of OPCAB (342 min),

and median duration of LDLT (620 min), respectively. Longer duration of combined surgery in this series compared to others (769 min) was mainly due to LDLT.<sup>[8]</sup> Average duration of LDLT<sup>[29,30]</sup> is  $615 \pm 99$  min, which is significantly higher than OLT<sup>[31]</sup> ( $\leq 300$  min). Other series had OLT from cadaveric donors, where median duration was 362 min [Table 2].<sup>[8]</sup>

In conclusion, in patients scheduled for LT, calcium score may be used to screen for CAD. Combined CABG-LT may be performed with acceptable outcomes in CTP class B and C cirrhosis. One-year mortality rate, ICU, and hospital stay after combined OPCAB and LDLT is comparable. Morbidity with OPCAB and LT is less than combined on pump coronary artery bypass surgery with LT. OPCAB with LT seems to be a feasible option in selected patients.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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