Original Article

Peri-operative extracorporeal membrane oxygenation in adult and pediatric living donor liver transplantation: a single-center experience

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Background: Extracorporeal membrane oxygenation (ECMO) is a potential rescue therapy for patients with acute cardiopulmonary dysfunction refractory to conventional treatment. In this study, we described the clinical profiles and outcomes of adult and pediatric living donor liver transplantation (LDLT) patients who received ECMO support during the peri-operative period.

Methods: From June 1994 to December 2020, eleven out of the 1,812 LDLTs performed at Kaohsiung Chang Gung Memorial Hospital required ECMO support: six for respiratory failure, three for cardiogenic shock, and two for refractory septic shock. Comparison between the survivor and non-survivor groups was made.

Results: The survival rate for liver transplantation (LT) patients on ECMO support is 36.4%—40% in adults and 33.3% in pediatrics, while the survival rate per indication is as follows: acute respiratory distress syndrome (ARDS) (50%), cardiogenic shock (33.3%), and sepsis (0%). Shorter durations of LT-to-ECMO and pre-ECMO mechanical ventilation were observed in the survivor group. On the other hand, we observed persistently elevated total bilirubin levels in non-survivors, while none of the survivors had aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels >1,000 U/L. A higher proportion of non-survivors were on concurrent continuous renal replacement therapy (CRRT).

Conclusions: Our experience has proven ECMO's utility during the peri-operative period for both adult and pediatric LDLT patients, more specifically for indications other than septic shock. Further studies are needed to better understand the factors leading to poor outcomes in order to identify patients who will more likely benefit from ECMO.

Keywords: Extracorporeal membrane oxygenation (ECMO); living donor liver transplantation (LDLT); respiratory failure; cardiogenic shock; septic shock

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Introduction

Advancements in surgical technique, peri-operative care, and post-transplant immunosuppression have significantly improved the outcomes of liver transplantation (LT) since its introduction in the 1960s. However, there remains a proportion of patients that develops peri-operative cardiopulmonary dysfunction refractory to conventional treatment, often leading to graft failure and patient demise (1-5).

Patients with acute and chronic liver diseases often have pre-existing multiple organ system impairment. They commonly present with coagulopathy, portal hypertension, and impaired immune system (2). In the peri-operative period, the added stress of the complex surgery and subsequent liver engraftment contributes to further physiological derangements predisposing these patients to cardiopulmonary failure, hemorrhage, and sepsis (3).

Prior to the utilization of extracorporeal membrane oxygenation (ECMO) in LT, the aforementioned conditions carried a very high mortality rate (2). Though initial reports showed dismal prognosis despite utilization of ECMO, technological innovations and accumulation of experience have resulted in better survival rates (6). ECMO is a potential rescue therapy for severe cardiopulmonary failure following LT for both adult and pediatric recipients with survival rates ranging from 28.6% to 68.2% (4-6). To date, a few studies have examined the role and outcome of ECMO in LT and due to the rarity of its use, the majority of these studies are case reports, case series and center-linked database analysis (4-9) (Table S1). In this study, we present the clinical profiles, indications for ECMO, and outcomes of eleven patients who presented with cardiorespiratory failure after adult and pediatric living donor liver transplantation (LDLT) in our center. We present this article in accordance with the STROCSS reporting checklist (10) (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-34/rc).

Highlight box

Key findings

- Survival rate for LDLT patients on ECMO support is 36.4%—adults (40%), pediatrics (33.3%).
- Survival rate per indication—ARDS (50%), cardiogenic shock (33.3%), refractory septic shock (0%).
- Shorter duration of LT-to-ECMO and pre-ECMO mechanical ventilation in survivors.
- Persistently elevated total bilirubin among non-survivors. None of the survivors had AST/ALT levels >1,000 U/L.
- Higher proportion of non-survivors on CRRT.

What is known and what is new?

- ECMO following LT is a viable rescue strategy for acute cardiopulmonary failure.
- This is the only study that focused solely on LDLT including both adult and pediatrics, as well as all indications for ECMO.

What is the implication, and what should change now?

- Every ECMO application in LT is unique and reporting of every incident is imperative to build body of experience to aid informed decision making for its further application.

Methods

Patient selection

From June 1994 to December 2020, 1,812 LDLTs were performed at the Kaohsiung Chang Gung Memorial Hospital, Taiwan. Throughout the study period, eleven patients received ECMO support during the peri-operative course. ECMO was employed in patients with acute cardiac or pulmonary failure due to potentially reversible causes. Patients who underwent either veno-arterial (VA) or veno-venous (VV) ECMO were included in the study. Patients with fluid overload or acute kidney injury (AKI) who were placed on concurrent continuous renal replacement therapy (CRRT) were also included in the study.

This study was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital [IRB No. 202300651B0(2304260003)]. Informed consent was obtained from all individual participants or patients' parents/guardians. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Post-transplant intensive care

After LDLT, patients are routinely transferred to the liver intensive care unit (LICU) under mechanical ventilatory support. The process of weaning and timing of extubation are tailored to individual patients. Close hemodynamic and cardiovascular monitoring is ensured. Biochemical, hematological and microbiological parameters are routinely monitored. Radiological investigations, including chest X-ray and hepatic vascular Doppler ultrasound are performed on a daily basis for the first two weeks. All patients in this study received standard immunosuppression and prophylactic antibiotics with the former being adjusted accordingly based on the patient's

overall clinical condition and laboratory parameters. Our standard immunosuppression constitutes steroids plus tacrolimus, and mycophenolate mofetil (MMF) for adults and cyclosporine and azathioprine for pediatrics. In the critically ill period especially in the presence of multi-organ failure (MOF), immunosuppression is drastically reduced to steroids alone. Patients who develop sepsis were managed initially with empiric antibiotics and subsequently shifted to agents against the identified pathogens based on *in vitro* susceptibility testing and recommendation of the co-managing infectious disease specialist. Patients are transferred to the general ward when clinical condition is deemed stable by the liver transplant team.

ECMO implantation, mode, and management

All ECMO cannulations are performed by an experienced cardiovascular surgery team at Kaohsiung Chang Gung Memorial Hospital. Capiox Emergency Bypass System (Capiox EBS/SP-101, Terumo Inc., Tokyo, Japan) and Medtronic bio console 560 devices were used for all patients. Details of the ECMO procedure and management have been described previously (11). Device insertion was performed by percutaneous puncture through the femoral VA route in adults while the internal carotid artery and internal jugular vein were accessed in pediatric patients.

In general, VV mode is utilized for patients with respiratory failure, while VA mode is considered in patients with cardiovascular dysfunction including those with septic shock. However, if a patient initially presenting with respiratory failure eventually exhibits hemodynamic instability, VA would be the mode of choice.

The management of patients on ECMO requires a multidisciplinary team involving the liver transplant surgeons, cardiovascular surgeons, anesthesiologists, intensivists, nurses, and perfusionists. The flow rate was adjusted to maintain mean blood pressure between 70 to 90 mmHg. Continuous heparin infusion was given to maintain an activated clotting time (ACT) between 150 and 180 seconds. The target was modified to 180 and 220 seconds in one patient with coronary artery metal stent for a ruptured left anterior descending (LAD) artery. The frequency for reassessing the ACT and adjusting the heparin dosage ranges from hourly to every eight hours depending on the clinical improvement of each patient after ECMO commencement. The heparin may be put on hold, decreased, or increased according to the latest coagulation parameters. In addition, fresh frozen plasma (FFP), cryoprecipitate and platelets are transfused as necessary. Echocardiography was performed daily to monitor cardiac function. ECMO weaning was considered when chest radiograph and lung compliance improved and hemodynamic remained stable in the absence of vasopressors. Ventilator support continued after weaning until recovery of spontaneous breathing.

Study design and statistical analysis

This is a retrospective observational study of the peri-operative use of ECMO in LDLT. Medical records of the patients were reviewed. All numerical data were reported as mean values with percentages or medians with ranges. The primary outcome was survival until discharge. Comparison between the survivor and non-survivor groups was made.

Results

Patient characteristics

Among the 1,812 LDLTs performed in our center between June 1994 to December 2020, eleven patients required ECMO support during the peri-operative course. The demographic profile and operative information are shown in *Table 1*.

There were five adults, including three males and two females, ranging from 49 to 54 years of age. Indications for LT were hepatitis B virus (HBV)-related liver disease in two, alcoholic liver disease in two, and chronic HBV-hepatitis C virus (HCV) co-infection in one. Hepatocellular carcinoma was present in two patients. The median Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) scores were 11 (range, 7–13) and 31 (range, 7–41), respectively. All adult recipients received a right lobe graft, median graft weight was 739 g (range, 626–869 g), median graft-to-recipient weight ratio (GRWR) was 1.15 (range, 0.83–1.49). The median blood loss was 9,700 mL (range, 1,800–35,000 mL).

There were six pediatric patients, including three males and three females, ranging from 5 to 48 months. Indications for LT were biliary atresia (BA) in four, ornithine transcarbamylase (OTC) deficiency in one and neonatal hepatitis (NH) in one. The median CTP and pediatric end-stage liver disease (PELD) scores were 10 (range, 7–12) and 20.5 (range, 13–39), respectively. Graft types included left lateral segment (n=3), hyper-reduced left lateral segment (n=1), left lobe (n=1), and segment 2 monosegment (n=1).

Table 1 Demographic profile of LDLT patients receiving ECMO

No.	Adult/Ped	Age (years)	Sex	Underlying liver disease	MELD/PELD	Indication for ECMO	Mode	Timing of ECMO from LT (days)	MV duration prior to ECMO (days)
1	Adult	54	M	HBV/HCC	31	ARDS	VA	1	1
2	Adult	52	M	ALD/HCC	40	Cardiogenic shock	VA	1	0
3	Ped	0.4	M	BA	13	ARDS	VV	7	7
4	Ped	1.8	F	BA	20	ARDS	VV	4	2
5	Adult	53	M	HBV	41	ARDS	VA	0	0
6	Ped	1.8	M	BA	16	Sepsis	VA	20	8
7	Ped	2	F	OTC deficiency	27	ARDS	VA	66	4
8	Ped	0.8	M	NH	39	Sepsis	VV	27	27
9	Ped	0.4	F	BA	21	ARDS	VV	15	1
10	Adult	54	F	HBV	7	Cardiogenic shock	VA	52	0
11	Adult	49	F	ALD	26	Cardiogenic shock	VA	41	3

LDLT, living donor liver transplantation; ECMO, extracorporeal membrane oxygenation; Ped, pediatric; MELD, model for end-stage liver disease; PELD, pediatric end-stage liver disease; LT, liver transplantation; MV, mechanical ventilation; M, male; F, female; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ALD, alcoholic liver disease; BA, biliary atresia; OTC deficiency, ornithine transcarbamylase deficiency; NH, neonatal hepatitis; ARDS, acute respiratory distress syndrome; VA, veno-arterial; VV, veno-venous.

Median graft weight was 275 g (range, 234–340 g), and median GRWR was 3.05 (range, 1.83–5.65).

Clinical features and outcomes are provided in *Table 2*. Seven patients were placed on VA-ECMO, for whom the indications were acute respiratory distress syndrome (ARDS) (n=3), cardiogenic shock (n=3), and septic shock (n=1). Four were placed on VV-ECMO, for ARDS (n=3) and septic shock (n=1). One patient (Patient 7) was placed on ECMO after re-transplantation which was performed 17 days after the first LDLT due to hepatic artery thrombosis (HAT). Most cannulations were performed at bedside in the LICU (n=9), while one was performed during LT upon graft reperfusion (Patient 5), and one in the cardiac catheterization laboratory (Patient 10).

Indications for ECMO

Respiratory failure (n=6)

ARDS was the most common indication for ECMO support. Six patients were placed on ECMO support due to ARDS. In four of them, ARDS was associated with transfusion-related acute lung injury (TRALI). Patients 1 and 5 suffered from significant intra-operative blood loss of 35,000 and 28,000 mL, and were transfused with leukocyte-poor red blood cells (LPR) (86, 40 units), FFP (46, 32 units), packed red blood cells (PRBC) (36, 0 units), cryoprecipitate (12, 48 units), and platelets (0, 48 units), respectively. Patient 1 developed ARDS on post-operative day one and had two re-explorations due to persistent bleeding, he succumbed to disseminated intravascular coagulopathy on post-operative day four. Patient 5 developed respiratory failure after the hepatic artery anastomosis, and hence, VA-ECMO was initiated intra-operatively; he was successfully decannulated on post-operative day five after staged biliary anastomosis. He was the only patient that ultimately survived among those with respiratory failure caused by TRALI. Patient 3 received urokinase on post-operative day one for portal vein stent thrombosis and was subsequently given tissue plasminogen activator (tPA) for re-thrombosis. Significant bleeding from the abdominal drains was noted, necessitating massive transfusion. Unfortunately, he died from MOF on post-operative day ten. Patient 9 suffered from significant internal bleeding post-operatively, requiring massive transfusion, consequently developing persistent hypoxia secondary to acute pulmonary edema. However, she developed intra-cerebral hemorrhage (ICH) on post-operative day 28, and the family decided to discontinue ECMO support three days later.

On the other hand, patient 4 developed acute pulmonary edema with respiratory acidosis unresponsive to nitric oxide

Table 2 Clinical features and outcomes of LDLT patients receiving ECMO

No.	Duration of ECMO (days)	Total bilirubin (mg/dL)		AST/ALT (U/L)		CRRT	ECMO-related complications	Outcome
		Start of ECMO	Prior to weaning/ death	Start of ECMO	Prior to weaning/ death			
1	2.96	1.8	7.1	107/78	1,574/344	Y	–	Expired
2	3.77	2.4	3.7	76/25	54/42	N	Bleeding at cannula site after removal	Alive
3	2.81	3.5	14.9	609/162	189/57	Y	–	Expired
4	24.28	9.9	3.1	52/44	46/40	N	Right leg cyanosis	Alive
5	4.69	29.2	24.9	128/182	259/328	Y	–	Alive
6	6.94	22.8	57	95/43	560/43	Y	–	Expired
7	15.60	6	11.3	406/569	67/57	N	Finger cyanosis	Alive
8	4.58	5.9	20.6	135/20	206/20	N	–	Expired
9	15.46	6.6	40.8	81/19	106/15	Y	ICH	Expired
10	8.16	0.8	3.5	30/13	57/98	Y	–	Expired
11	1.02	8	21.4	104/85	1,518/304	Y	–	Expired

LDLT, living donor liver transplantation; ECMO, extracorporeal membrane oxygenation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRRT, continuous renal replacement therapy; N, no; Y, yes; ICH, intra-cerebral hemorrhage.

and conventional ventilatory support, while patient 7 who underwent re-transplantation for HAT developed ARDS secondary to pancreatitis. Both patients were successfully weaned off ECMO and remain alive to date.

Cardiogenic shock (n=3)

Patient 2 who had normal cardiac function based on pre-operative transthoracic echocardiogram (TTE) and myocardial perfusion scan, suffered from sudden cardiac arrest on post-operative day one. Following successful cardiopulmonary resuscitation, he survived after three days of VA-ECMO support. Patient 10 was a known diabetic with normal cardiac function on pre-operative TTE; she suffered from ST-elevation myocardial infarction (STEMI) post-operatively. Coronary angiography revealed spontaneous dissection of the LAD artery for which metal stents were placed. ECMO was initiated thereafter in combination with intra-aortic balloon pump (IABP) as well as CRRT. However, she was not weaned off ECMO due to diffuse left ventricular hypokinesia. Patient 11 had an underlying grade III diastolic left ventricular dysfunction. She was started on amiodarone for premature ventricular contractions and ventricular tachycardia on post-operative day five, but eventually developed altered consciousness and hypotension despite inotropic support. Coronary angiography showed poor left ventricular contractility and she was subsequently placed on ECMO support. Unfortunately, she succumbed to fatal arrhythmia the next day.

Refractory septic shock (n=2)

ECMO was initiated in two pediatric patients with refractory septic shock. Prior to LT, Patient 8 was treated with meropenem for pneumonia. Post-operatively, he developed central line-associated bloodstream infections (CLABSI) and pneumonia. *Staphylococcus epidermidis* and *Klebsiella pneumoniae* were isolated from the blood and central venous catheter (CVC) tip cultures. Due to uncontrolled sepsis, he had multiple failed attempts at mechanical ventilatory weaning, eventually resulting in MOF. Patient 6 developed peritonitis and septic shock from a jejuno-jejunostomy leak, which was repaired surgically. Unfortunately, both patients died of MOF. Both patients had persistently elevated C-reactive protein (CRP) after ECMO initiation.

Comparison of survivors and non-survivors

Four out of the eleven patients (36.4%), including two adults and two pediatric patients, were successfully weaned

from ECMO and survived until discharge. Two of the four survivors were on mechanical ventilation for less than 24 hours prior to ECMO initiation (50%) as compared to one out of seven in the non-survivor group (14.3%). Timing of cannulation ranged from 0 to 66 post-LT days for the survivors and 1 to 73 post-LT days for the non-survivors. Duration of cannulation for the survivors ranged from 3.8 to 24.3 days while the median timing of extubation was 12.5 days after decannulation (range, 2–32 days). Weaning was not attempted in all non-survivors (63.6%) and ECMO support was continued until death.

Liver function was compared between the two groups. Total bilirubin increased from the pre-cannulation level and remained elevated for all non-survivors. For the survivors, the total bilirubin levels at decannulation ranged from 3.1 to 24.9 mg/dL. Two of the four survivors had decreased total bilirubin levels prior to decannulation. In addition to bilirubin levels, the following parameters were compared between the survivors and non-survivors upon decannulation: aspartate aminotransferase (AST) (46–259 *vs.* 57–1,574 U/L), alanine aminotransferase (ALT) (40–328 *vs.* 15–344 U/L), and international normalized ratio (INR) (1.26–1.72 *vs.* 1.76–5.3). After initiation of ECMO, 57.14% and 28.57% in the non-survivor group had AST and ALT levels >1,000 U/L, respectively, compared to 0% in the survivor group.

In all non-survivors, immunosuppressants were stopped prior to or upon initiation of ECMO. On the other hand, one survivor was maintained on standard immunosuppression (Patient 2) during ECMO while another was maintained on single-agent immunosuppression (Patient 4).

Renal function was compared between the two groups. Seven patients were placed on concurrent CRRT (63.6%). In the survivor group, although three of four had elevated BUN levels (14–37 mg/dL), only one patient with hepatorenal syndrome was placed on CRRT (25%). On the other hand, five of the seven non-survivors had elevated BUN levels (14–70 mg/dL) with higher levels compared to the survivor group. Six of the seven non-survivors were placed on CRRT (85.7%).

Complications

In the survivor group, three patients developed ECMO-related complications which included bleeding at cannula site after removal, right leg cyanosis, and right finger cyanosis. Only the patient with right finger cyanosis required immediate removal of ECMO. There was resolution of all complications upon ECMO removal without surgical management. As mentioned previously, one patient in the non-survivor group suffered from ICH, a fatal complication associated with ECMO.

Discussion

The utility of ECMO in the peri-operative care for LT patients has been demonstrated in previous studies (5,7-9). However, data related to indications, contraindications, and use of this treatment modality remains scarce. Every ECMO application in LT is unique and the reporting of every incident to build a body of experience would benefit the transplant community and guide future applications of ECMO in these patients (12,13).

With careful patient selection, ECMO is rarely needed in the LT setting. In our center, 90% of LTs are from living donors and the three-year survival rate after LDLT is 92% with only 0.6% requiring peri-operative ECMO support (14). Nonetheless, our findings suggest that ECMO plays a crucial role in the management of this subset of patients who would have not survived otherwise. It is particularly effective if the reversible cause of the cardiopulmonary failure is promptly recognized and ECMO is instituted in a timely manner (4).

ECMO for cardiovascular failure

The more commonly reported causes of peri-operative cardiovascular failure in LT include reperfusion-associated right ventricular failure, intra-cardiac thrombosis, and massive pulmonary embolism (6). In our study, three patients suffered from cardiogenic shock leading to initiation of ECMO. Liu *et al.* mentioned that as much as 50% LT recipients with cirrhosis develop cardiac dysfunction within the first week of LT. The presence of an underlying cardiac pathology in these patients is characterized by impaired inotropic and chronotropic responsiveness to stress in addition to an altered diastolic relaxation (15). An underlying irreversible or chronic disease such as presence of pre-operative ventricular dysfunction in one of our patients translated to an unfavorable outcome. The other non-survivor had normal pre-operative cardiac function but developed severe myocardial infarction post-operatively with diffuse ventricular hypokinesia on TTE. Several reports have demonstrated that even in the presence of profound cardiogenic shock, ECMO has been proven to be a life-saving strategy both in the non-transplant and

transplant setting in a certain subset of patients (11,16,17).

ECMO for respiratory failure

Peri-operative respiratory failure among LT recipients has been associated with the following conditions: hepatorenal syndrome, ARDS, pneumonia, aspiration pneumonitis, and pulmonary hemorrhage. Six of our patients developed ARDS and this was attributed to TRALI, pancreatitis and acute pulmonary edema secondary to fluid overload (6,18). Persistent hypoxemic respiratory failure results in imminent MOF, including failure of the newly transplanted liver (4,9). Post-operative ARDS involves an acute inflammatory cascade that leads to pulmonary edema. The profound hypoxemia results in cellular damage subsequently increasing the permeability of the pulmonary capillaries, ultimately leading to accumulation of fluid in the interstitial space (8). The critical role of liver function in the pathogenesis and resolution of ARDS substantially influencing the prognosis of these patients is increasingly being recognized (19). Presently, there is mounting evidence that ECMO is an effective salvage therapy for patients with refractory pulmonary dysfunction, serving as a supportive measure while the failing lungs recover over time.

ECMO for refractory septic shock

Infection is the leading cause of morbidity and mortality after LT, estimated to occur in approximately 48.1% of patients (18,20). Several risk factors predisposing transplant patients to infections have previously been identified and these include: pre-transplant ascites, pre- and post-transplant dialysis, re-operation, wound infection, HAT, and reconstruction with Roux-en-Y choledochojejunostomy (20,21). Another important risk factor for post-transplant infection is pre-transplant infection. According to Kim *et al.*, even if pre-transplant infection is adequately treated, the risk for post-transplant infection with positive cultures may still be as high as 70.4% (21).

Both of our septic patients received Roux-en-Y anastomosis. One of them was treated for pneumonia pre-operatively while the other was re-operated for jejuno-jejunostomy leak post-operatively, putting both of them at increased risk for post-transplant infections. *Klebsiella pneumoniae* was isolated from the blood and CVC tip cultures of one of these patients. Bacteremia-associated mortality ranges from 10–52% in post-transplant patients and it has been found to be even higher in the presence of 'ESKAPE' pathogens—*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* species (5).

In addition to the aforementioned risk factors, biochemical parameters that could be used to reflect response to ECMO support have also been described. One study reported that CRP levels remained elevated in the non-survivor group (5). This was also seen among the two septic patients in our study.

Regarding the timing of ECMO for septic patients, it has been proposed that ECMO should be considered once there is evidence of organ hypoperfusion despite adequate intravascular volume (5). In a study by Park *et al.*, there were no survivors in patients who were placed on ECMO after 30.5 hours from the onset of septic shock (9). Lee *et al.* reported a 25% survival rate despite ECMO use for post-transplant septic shock in contrast to a 44.4% survival rate in a series by Park *et al.* on ECMO for respiratory failure (5,9). A more recent study has reported a one-year survival rate of 10.3% for LT recipients placed on ECMO for refractory shock (22). However, it is also important to note that all non-survivors in the latter study died of overwhelming sepsis. Similarly, we also noted better survival rates when ECMO was used for respiratory failure (50%) and cardiogenic shock (33.3%), as compared to septic shock (0%). To improve outcomes for these patients, timely initiation of appropriate antibiotics is of paramount importance. For selected patients, ECMO has become a new treatment option for sepsis albeit lower survival rates compared to other indications for ECMO. Indeed, there is a need to better understand the factors leading to poor outcomes in ECMO support for refractory septic shock as well as objective parameters to determine who would be more likely to benefit from ECMO. Definition of the patient selection criteria for ECMO utilization may help provide better care for septic LT recipients (5,9,23).

Timing of ECMO

Better outcomes were seen in patients who required ECMO within 24 to 48 hours after LT and it was suggested that delay in the initiation of ECMO could lead to irreversible organ damage and eventual patient demise (4,6,9,24). In our study, 50% in the survivor group had early ECMO initiation as compared to 14.3% among non-survivors. In addition to the time from LT to ECMO, a study by Park *et al.* showed that patients with shorter pre-ECMO mechanical ventilation time had improved survival which was also seen

in our study (9). No other demographic or pre-operative clinical characteristics was shown to be associated with failure of weaning from ECMO aside from longer time from LT to ECMO and length of time on mechanical ventilator support prior to ECMO. These findings suggest earlier initiation is important prior to development of other organ dysfunctions.

Immunosuppression

LT recipients present a distinct set of challenges for ECMO. Immunosuppression has been shown to be an independent risk factor for ECMO-related mortality. It enhances the patient's susceptibility to *de novo* infections as well as reactivation of pre-existing latent infections (9,18,25). In a series by Goussous *et al.*, immunosuppression was decreased by adjusting levels according to biopsy results and liver function tests and rejection was addressed by increasing calcineurin inhibitors while avoiding steroid pulse therapy (2). On the contrary, there was no reduction in immunosuppression in another report by Braun *et al.* (4). Two of seven patients succumbed to fungemia in the series with lowered immunosuppression and one of five patients died of sepsis in the latter (2,4). In our study, dose adjustments for immunosuppression were based on the clinical and biochemical status as well as trough level of each patient. Only one patient developed acute cellular rejection two months after ECMO initiation. This is unlikely related to the utilization of ECMO, since this patient was maintained on standard immunosuppression for the total duration he was placed on ECMO support.

Anticoagulation

Similar to immunosuppression, there is still no consensus regarding anticoagulation in LT recipients on ECMO support. These patients generally require systemic anticoagulation to prevent clotting of the circuit but this must be balanced against the risk of bleeding especially during the early post-operative period. Some authors used the standard post-LT heparin regimen while some decreased the dosage and others held the anticoagulation for days to weeks in patients with coagulopathy and bleeding (4,18,26). Most authors noted no apparent adverse effects for the various anticoagulation protocols employed. Conversely, one study reported that 58% of patients needed re-operation for bleeding after systemic anticoagulation (18). In our study, there were two patients with bleeding as complications. Anticoagulation was discontinued for one with bleeding at the cannula site, and for the patient with ICH, the patient's family decided to withdraw life support after being appraised of the irreversible outcome.

Liver function

The interpretation of liver function tests in post-transplant recipients on ECMO may be challenging. There is a concern that ECMO can itself cause liver dysfunction; its initiation has been associated with reversible cholestasis and duration of ECMO is considered an independent risk factor for cholestasis (3,5). Other reports have attributed the cholestasis to the lack of physiologic pulsatile flow for the VA mode or simply associated with the acute illness and sepsis (18). One study noted an increase in total bilirubin level in 65% of patients upon cannulation but with normalization after 5 days in two-thirds of these patients (27). In our study, the total bilirubin levels normalized among the survivors in 17–25 days from the date of ECMO initiation. Elevated total bilirubin level has been used as a predictor of mortality among ICU patients undergoing liver resection. Some authors have suggested that liver function may be used to prognosticate long-term survival in patients receiving ECMO (3,5,22). For all non-survivors in our series, total bilirubin increased after cannulation and remained elevated while on ECMO. In addition, the liver enzymes of our patients ranged from normal to varying degrees of elevation. For the non-survivors, 57.14% had AST levels >1,000 U/L while 28.57% had ALT levels >1,000 U/L. None of the survivors had liver enzyme levels greater than 1,000 U/L. In contrast, one series reported that 47% of their patients on ECMO had AST and/or ALT levels greater than 1,000 U/L (27). Previous reports have associated the improvement in transaminase levels after ECMO initiation with resolution of acidosis, improved oxygenation, and hemodynamic stability (2).

CRRT

Aside from liver dysfunction, it is not uncommon for patients who receive ECMO in the setting of acute cardiorespiratory failure to develop AKI, both due to the circulatory collapse and transient hypoxemia. In fact, patients with chronic liver failure may experience progressive renal dysfunction and thus are at even higher risk for AKI (18). Goussous *et al.* reported that acute renal failure requiring hemodialysis developed in 85.7%

of patients on ECMO (2). Several studies have reported improved outcomes with post-LT ECMO in patients who received CRRT (3,4,9). In patients on VA-ECMO support, CRRT helps in volume optimization by providing afterload reduction to ensure distal perfusion, particularly to the newly implanted graft. CRRT has also been shown to improve caloric intake, reduce the use of diuretics in comparison to ECMO alone (4). In our study, seven patients were placed on concurrent CRRT (63.6%), one from the survivor group (25%) and six from the non-survivor group (85.7%). It appears to be contradictory to the results from previous studies, probably because the use of renal replacement therapy in LT patients receiving ECMO support likely reflects the overall critically ill state of these patients.

Complications

Previously reported ECMO-related complications include bleeding, thromboembolism, and stroke. Four of our patients experienced ECMO-related complications—three patients survived and one who developed ICH was unable to wean off ECMO support. One report mentioned that re-operation was performed in 57.1% of patients due to bleeding, as opposed to this study wherein no patient required re-operation for ECMO-related bleeding (3). On the other hand, stroke, and other neurologic complications in patients on ECMO are reportedly associated with VA-ECMO rather than VV-ECMO. Neurologic complications occur in approximately 13% of VA-ECMO patients while VV-ECMO has been associated with a 5% risk of ICH (18). There is no consensus for management of stroke for patients on ECMO after LT, and hence, the risks and benefits of anticoagulation in patients with stroke must be carefully weighed (18,25,28). Cardiopulmonary evaluation should be performed frequently to determine the timing of weaning to avoid the development of complications. In a study by Yoon *et al.*, 13.7% of LT recipients placed on peri-operative ECMO underwent reapplication of ECMO after weaning within the same hospitalization and only 60% of these patients were successfully weaned off again (22). On the contrary, we had no patient in need of re-cannulation. Reassessment of the clinical parameters for weaning is warranted in order to identify factors leading to reapplication of ECMO to prevent premature weaning in succeeding patients.

To the best of our knowledge, this is the only study that focused solely on LDLT, including both adult and pediatric age groups. Furthermore, we have also included all indications for ECMO as well as described potential parameters that can be used in formulating a selection criterion and identifying prognostic factors for these patients. In summary, the main findings in our study are as follows: (I) survival rate for LDLT patients on ECMO support is 36.4%—40% in adults and 33.3% in pediatrics; (II) survival rate per indication—ARDS (50%), cardiogenic shock (33.3%), and refractory septic shock (0%); (III) shorter duration of LT-to-ECMO and pre-ECMO mechanical ventilation were observed in the survivor group; (IV) persistently elevated total bilirubin levels among non-survivors; (V) AST and ALT levels >1,000 U/L occurred in 57.1% and 28.6% in non-survivors, respectively, compared to 0% in survivors; (VI) higher proportion of non-survivors were on CRRT. The ability to demonstrate relatively rapid recovery after instituting ECMO due to the arrest or reversal of the initial insult appears to be associated with better survival.

The retrospective nature, single-center experience, and the small number of patients in this study limit its strength and generalizability. Nevertheless, we intend to add our experience to the growing literature on ECMO in LDLT to aid in informed decision making for its future application.

Conclusions

ECMO provides temporary support to failing cardio-pulmonary function unresponsive to conventional treatment modalities. Our experience has proven its utility during the peri-operative period for both adult and pediatric LDLT patients, more specifically for indications other than refractory septic shock. Timely recognition and prompt institution of ECMO is crucial in carefully selected cases. A multidisciplinary approach is integral in the management of these patients. Further studies are needed to better understand the factors leading to poor outcomes in order to identify patients who will more likely benefit from such treatment. Each patient should be assessed on a case-by-case basis and in the context of the individual center's experience.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital [IRB No. 202300651B0(2304260003)]. Informed consent was obtained from all individual participants or patients' parents/guardians.

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Supplementary

Table S1 Literature review of ECMO in liver transplant (case series and multi-center linked database)

Author	Year	Country	Patients included	Patient type	Type of LT	Mode	ECMO indication	Survival rates
Nandhabalan *et al.*	2016	United Kingdom	3	Pediatrics	DDLT	VV [3]	Pre-LT [2] ARDS [1]	2/3
Braun *et al.*	2019	United States	8	Adult	DDLT	VV [4]; VA [4]	Massive PE; Right heart failure; Hypoxemic respiratory failure (1/3–HPS); Hepatic congestion from suprahepatic IVC occlusion	3/8
Goussous *et al.*	2019	United States	7	Adult	DDLT	VV [4]; VA [3]	ARDS [2]; HPS; Aspiration; RV thrombus [2]; Massive PE	5/7
Lee *et al.*	2017	South Korea	8	Adult	DDLT/LDLT	VA [8]	Septic shock	2/8
Park *et al.*	2012	South Korea	18	Adult	DDLT/LDLT	VV [18]	ARDS [6]; Pneumonia [12]	8/18
Ziogas *et al.*	2021	United states	34	Pediatrics	LT type not specified. Type of graft was described as: Whole/ partial/split	Not specified	Pneumonia [6]; HPS [5]; ARDS [3]; Septic shock [3]; Pulmonary hemorrhage [3]; Pulmonary edema [1]; Portopulmonary [1]; Heart failure [1]; Indication for ECMO not available in 14 patients	19/34
Yoon *et al.*	2023	South Korea	109	Adult	DDLT/LDLT	VA [58]; VV [51]	Cardiogenic shock [34]; Respiratory failure [51]; Septic shock [34]	47/109
Seo *et al.*	2015	South Korea	32	Adult	Not specified	VV [32]	ARDS	5/32
Levesque *et al.*	2019	France	4	Adult	Not specified	VV [3]; VA [1]	Refractory Hypoxemia [3]; Right heart failure [1]	3/4
Choi *et al.*	2012	South Korea	9	Adult	DDLT/LDLT	VV [9]	ARDS [4]; Pneumonia [5]	4/9

Number in square brackets indicate the number of patients included for each mode and each ECMO indication.

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