9-1-2021

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Immediate Postoperative Extubation Decreases Pulmonary Complications in Liver Transplant Patients

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Background. Fast-track anesthesia in liver transplantation (LT) has been discussed over the past few decades; however, factors associated with immediate extubation after LT surgery are not well defined. This study aimed to identify predictive factors and examine impacts of immediate extubation on post-LT outcomes. **Methods.** A total of 279 LT patients between January 2014 and May 2017 were included. Primary outcome was immediate extubation after LT. Other postoperative outcomes included reintubation, intensive care unit stay and cost, pulmonary complications within 90 days, and 90-day graft survival. Logistic regression was performed to identify factors that were predictive for immediate extubation. A matched control was used to study immediate extubation effect on the other postoperative outcomes. **Results.** Of these 279 patients, 80 (28.7%) underwent immediate extubation. Patients with anhepatic time >75 minutes and with total intraoperative blood transfusion ≥12 units were less likely to be immediately extubated (odds ratio [OR], 0.48; 95% confidence interval [CI], 0.26-0.89; $P=0.02$; OR, 0.11; 95% CI, 0.05-0.21; $P<0.001$). The multivariable analysis showed immediate extubation significantly decreased the risk of pulmonary complications (OR, 0.34; 95% CI, 0.15-0.77; $P=0.01$). According to a matched case-control model (immediate group [n=72], delayed group [n=72]), the immediate group had a significantly lower rate of pulmonary complications (11.1% versus 27.8%; $P=0.012$). Intensive care unit stay and cost were relatively lower in the immediate group (2 versus 3 d; $P=0.082$; \$5700 versus \$7710; $P=0.11$). Reintubation rates (2.8% versus 2.8%; $P>0.9$) and 90-day graft survival rates (95.8% versus 98.6%; $P=0.31$) were similar. **Conclusions.** Immediate extubation post-LT in appropriate patients is safe and may improve patient outcomes and resource allocation.

(*Transplantation* 2021;105: 2018–2028).

INTRODUCTION

The practice of fast-track anesthesia, which has become synonymous with early or immediate postoperative extubation, was first described in the context of cardiac surgery in the 1970s. Before this, postoperative ventilation was the standard of care in major surgeries, including liver transplantation (LT). Since then, several studies have shown the practice of fast-tracking to be safe and cost effective.[1,2] In the 1990s, this practice was applied to LT patients.[3,4]

Benefits of early extubation in LT patients include decreased pulmonary complications, intensive care unit (ICU) and hospital stay, cost, and potentially improved graft function. [3,4] Many LT patients have some baseline pulmonary dysfunction secondary to liver disease. Prolonged mechanical ventilation in these patients is a well-defined risk factor for further pulmonary complications. Pulmonary complications from mechanical ventilation have been shown to negatively affect morbidity and mortality in LT patients.[5,6]

Although the practice of fast-track anesthesia in LT patients has been in place for over 2 decades, no uniform criteria for successful immediate postoperative extubation exists.[7] In our study, we aim to identify predictive factors for immediate extubation post-LT and assess how this practice impacts clinical outcomes.

Received 6 March 2020. Revision received 11 June 2020.

Accepted 3 July 2020.

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The authors declare no funding or conflicts of interest.

C.A., Y.M., M.S., A.Y., J.E., and S.N. participated in research design. C.A, Y.M., M.S., V.F, and S.N. participated in the writing of the article. D.G., A.Y, and M.A. participated in the performance of the research. D.G., M.A., A.Y, J.E, and S.N. participated in the critical review of the article. C.A, Y.M., M.S., V.F., and S.N. participated in data analysis.

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ISSN: 0041-1337/20/1059-2018

DOI: 10.1097/TP.0000000000003450

MATERIALS AND METHODS

Study Design

After institutional review board approval, we retrospectively analyzed LT cases performed between 2014 and 2017 at a single tertiary medical center. Patient charts were reviewed using the electronic medical recording system. All LT patients were included except for retransplant patients. Patients undergoing liver-kidney transplantation, multivisceral transplantation, those who were already intubated before LT, and those who died intraoperatively were excluded. Primary outcome was immediate extubation after LT. Secondary outcomes included reintubation rates, length of ICU stay, ICU cost, respiratory complications within 90 postoperative days (POD), and graft survival at 90 days.

Anesthetic Management

Before LT surgery, patients were assessed by the anesthesia and surgery teams, and Karnofsky score and degree of hepatic encephalopathy were determined. All patients received general anesthesia with endotracheal intubation, standard American Society of Anesthesiologists monitoring, invasive arterial blood pressure monitoring, central venous pressure monitoring, pulmonary artery pressure monitoring, and transesophageal echocardiography. Central venous access was obtained in every patient using a Multi-Lumen Access Catheter. Dialysis access was obtained in patients who required intraoperative continuous venovenous hemofiltration. Balanced anesthesia with inhalational agents, opioids, and muscle relaxants was decided upon by the anesthesiologist. A standardized ventilation setting protocol of tidal volume of 6–8 mL/ideal body weight and positive end-expiratory pressure >2 cmH_2O was used. Intraoperative fluid, blood product transfusion, and vasopressors were managed based on the clinical judgement of the anesthesiologist utilizing intraoperative thrombelastometry, arterial blood gases, coagulation test results, and transesophageal echocardiography.

Extubation Criteria and Definition of Immediate Extubation

Immediate postoperative extubation was defined as tracheal extubation in the operating room. General extubation parameters including reversal of muscle relaxant, ability to achieve adequate tidal volume, absence of hypercapnia and hypoxia, no significant acid/base derangement, and ability to follow commands were taken into account. Threshold for oxygenation capacity was PaO_2/FiO_2 ratio >200. Factors unique to LT such as minimal pressure requirement, intraoperative transfusion requirement, absence of severe coagulopathy, and indices on reasonable graft function such as coagulation test values, serum lactate levels, and bile production were also taken into consideration. The decision to extubate was comprehensively made by the anesthesiologist as well as the surgical team. When patients remained intubated, timing of extubation was determined by the ICU team.

Surgical Management

Donor livers were flushed with CUSTODIOL Histidine–Tryptophan–Ketoglutarate solution (Essential Pharmaceuticals, LLC., Newtown, PA). The liver graft was reperfused after reconstruction of hepatic vein and portal vein and hepatic artery reconstruction followed. In the hepatic vein reconstruction, the piggyback technique was preferentially used, and the standard inferior vena cava (IVC) replacement (bicaval technique) and side-to-side cavocavostomy were used at the discretion of the surgeon and based on intraoperative judgement. Cold ischemia time (CIT) starts with donor cross clamping and ends with the removal of the liver from the cold preservative solution before implantation. Warm ischemia time (WIT) was defined from the time when the liver was taken out of the cold preservative solution, in preparation for implantation, until the portal reperfusion. Anhepatic time was defined from clamping of the portal vein to portal reperfusion.

Definitions of Pulmonary Complications

Pulmonary complications post-LT were identified and categorized based on consensus definitions by the Standardized Endpoints for Perioperative Medicine and the Core Outcome Measures in Perioperative and Anesthetic Care group, which included pneumonia and symptomatic pleural effusion or pulmonary edema requiring treatment and escalation of respiratory support.[8]

Definition of Cost

Total ICU cost was assessed for all patients. Parameters taken into account included total hospital cost for the first admission post-LT, cost of the LT surgery itself, cost for any reoperations post-LT, ICU cost post-LT, and total cost for readmission within 3 months of discharge after LT. Costs are listed in standard US dollars.

Statistical Analysis

Data were analyzed using median and interquartile range (IQR) for continuous variables and using percentage for discrete variables. Continuous variables were analyzed using Mann-Whitney *U* test, and discrete variables were analyzed using chi-square tests. Patients were censored on the last day of follow-up. The possible risk factors (covariates) included the recipient's demographics (age, gender, and ethnicity), body mass index (BMI), model for end-stage liver disease (MELD) score at transplant, severity of hepatic encephalopathy, Karnofsky score, cause of primary liver disease, and hepatocellular carcinoma as a coexisting diagnosis; donor factors included donor type, demographics (age, gender, and ethnicity), and BMI; operative factors included CIT, WIT, anhepatic time, intraoperative blood transfusion, operative time, intraoperative vasopressor requirement (none, single, or multiple), and hepatic vein reconstruction technique (IVC replacement versus preservation). In terms of a cutoff value of Karnofsky score, patients were categorized into 2 groups; 10%–30% (moribund, very sick, and severely disabled) and 40%–100%. BMI of 20, 25, and 30 were used as cutoff values. Cutoff values for anhepatic time and intraoperative total amount of blood transfusion (packed red blood cell, fresh frozen plasma, and autologous transfusion) were decided based on receiver operating characteristic curve analysis. Anhepatic time of 75 minutes and intraoperative total amount of blood transfusion of 11.5 units were determined to provide the highest Youden's index to predict immediate extubation. MELD score, CIT, WIT, and operative time did not have a clear threshold to predict immediate extubation based on an receiver operating characteristic curve analysis; therefore, MELD score of 20 and 30, CIT of 6 and 8 hours, WIT of 30 minutes, and operative time of 6 and 8 hours were used to categorize patients.

Given a large number of covariates were described, we further selected 14 factors based on clinical relevance,[4,9,10] including 7 recipient characteristics (age, BMI, hepatitis C status, MELD score, encephalopathy grade, and Karnofsky score before operation), 1 donor variable (donor type), and 6 operative factors (CIT, anhepatic time, WIT, transfusion, operative time, and multiple pressor requirement). Logistic regression with a backward model selection was considered to study the factors predictive effect on the outcome of immediate extubation. Before the multivariable analysis, we estimated correlation among the factors. The highly correlated factors were included in the multivariable model 1 at the time along with the other covariates. To ensure the model stability and robustness, analysis was restricted to have the maximum of 8 variables in the first multivariable model. The variables were retained in the model if they had significant risk for immediate extubation with P value < 0.05, after the backward model selection. The final model was determined based on model goodness of fit (eg, C-index) and clinical interpretation. Odds ratio (OR) and its 95% confidence interval (CI) were estimated for the factors retained in the final multivariable model. The same analytical approach was used for outcome of pulmonary complications.

Delayed and immediate extubation groups were matched using exact matched controls, which considered MELD score, Karnofsky score, status of encephalopathy, donor type, operative time, intraoperative blood transfusion, CIT, and anhepatic time. Kaplan-Meier method and log-rank test were used to compare graft survival rates between the 2 groups. Significance was set at 0.05. All statistical analyses were performed using SPSS version 25 (IBM, Chicago, IL) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 341 patients underwent LT between January 2014 and May 2017. Of these, the following patients were excluded; 12 who underwent retransplantation, 36 who underwent liver-kidney transplantation, 6 who underwent multivisceral transplantation, 5 who were intubated pre-LT, 1 who died without extubation post-LT, and 2 who died intraoperatively; thus, we arrived at our study cohort of 279 patients (Figure 1). Eighty patients (28.7%) underwent immediate extubation.

Patient Characteristics

Demographics among the immediate and delayed extubation groups are shown in Table 1. The median age of patients in the immediate extubation group was 60.0 years (IQR [54.5, 64.0]) and 58.5 years (IQR [51.8, 64.0]) in the delayed extubation group ($P = 0.284$). Males made up 66.2% of the immediate extubation group and 63.8% of the delayed extubation group ($P = 0.782$). Race was also found to be similar among the groups ($P = 0.913$) (Table 1). The delayed extubation group had a significantly higher median MELD score (21.0, IQR [15.0, 28.0] versus 17.0, IQR [10.8, 24.0]; $P = 0.001$), were more likely to have a lower Karnofsky score ($P = 0.039$), had longer median CIT (297 min, IQR [255, 362] versus 269.5 min, IQR [231.8, 334.8]; $P = 0.003$), longer median anhepatic time (78 min, IQR [63.0, 90.3] versus 72 min, IQR [60.0, 82.0]; $P = 0.024$), long median operative time (7.0 h, IQR [5.9, 8.4] versus 6.4 h, IQR [5.2, 7.3]; $P < 0.001$), and received a larger amount of intraoperative blood transfusions (15 units, IQR [8.0, 26.0] versus 5 units, IQR [2.0, 10.0]; $P < 0.001$).

Factors Associated With Immediate Extubation

The univariable analyses showed higher MELD score, presence of hepatic encephalopathy, lower Karnofsky score, longer CIT, longer anhepatic time, longer operative time, larger amount of intraoperative transfusion, requirement of multiple vasopressors, and use of IVC preservation techniques (ie, piggyback technique, side-to-side cavocavostomy technique) significantly decreased the likelihood of immediate extubation (OR < 1), whereas living donor LT significantly increased the likelihood compared with LT using donation after neurological determination of death donors (Table 2).

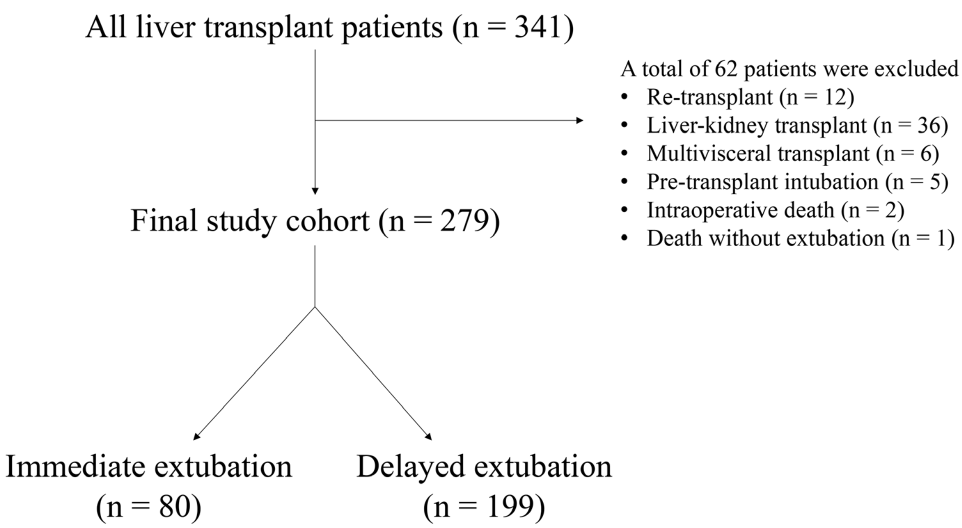

FIGURE 1. Patient selection. A total of 341 patients underwent LT between January 2014 and May 2017. Of these, 5 patients who were already intubated pre-LT, 12 who underwent retransplantation, 36 who underwent liver-kidney transplantation, 6 who underwent multivisceral transplantation, 1 who died without extubation post-LT, and 2 who died intraoperatively were excluded; thus, we arrived at our study cohort of 279 patients. LT, liver transplantation.

TABLE 1.

Comparisons of patient characteristics between the delayed and immediate extubation groups

Factor[a]		Timing of extubation: Delayed (in intensive care unit) N=199	Timing of extubation: Immediate (in operating room) N=80	*P*
Recipient age (y)		60.0 [54.5, 64.0]	58.5 [51.8, 64.0]	0.284
Recipient gender (%)	Male	127 (63.8)	53 (66.2)	0.782
Recipient ethnicity (%)	White	164 (82.4)	68 (85.0)	0.913
	Black	20 (10.1)	9 (11.2)	
	Others	15 (7.5)	3 (3.8)	
Hepatitis C (%)		65 (32.7)	30 (37.5)	**0.039**
Hepatocellular carcinoma (%)		53 (26.6)	37 (46.2)	0.083
Recipient BMI		29.2 [26.2, 33.7]	28.1 [25.6, 31.8]	0.229
MELD score		21.0 [15.0, 28.0]	17.0 [10.8, 24.0]	**0.001**
Encephalopathy	Absent	43 (21.6)	30 (37.5)	**0.01**
	Present	156 (78.4)	50 (62.5)	
Karnofsky score	40%–100%	153 (81.4)	67 (91.8)	**0.039**
	10%–30%	35 (18.6)	6 (8.2)	
Donor type (%)	Donation after neurological determination of death	168 (84.4)	66 (82.5)	**0.003**
	Donation after circulatory death	21 (10.6)	2 (2.5)	
	Living	10 (5.0)	12 (15.0)	
Donor age (y)		42.0 [29.0, 54.0]	45.0 [30.8, 55.3]	0.404
Donor gender (%)	Male	127 (63.8)	53 (66.2)	0.782
Donor BMI		28.0 [23.6, 31.8]	27.6 [23.9, 31.4]	0.689
Donor ethnicity (%)	White	162 (81.4)	63 (78.8)	0.842
	Black	28 (14.1)	14 (17.5)	
	Others	9 (4.5)	3 (3.7)	
Cold ischemia time (min)		297.0 [255.0, 362.0]	269.5 [231.8, 334.8]	**0.003**
Warm ischemia time (min)		38.0 [32.0, 44.0]	35.0 [29.8, 42.3]	0.223
Anhepatic time (min)		78.0 [63.0, 90.3]	72.0 [60.0, 82.0]	**0.024**
Total amount of intraoperative transfusion (unit) (PRBC, FFP, autologous)		15.0 [8.0–26.0]	5 [2.0–10.0]	**<0.001**
Operative time (h)		7.0 [5.9, 8.4]	6.4 [5.2, 7.3]	**<0.001**
Number of intraoperative maximum vasopressor		2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	**0.027**
Hepatic vein reconstruction	IVC preservation[b]	188 (73.4)	68 (26.6)	**0.005**
	IVC replacement	10 (45.5)	12 (54.5)	

P values <0.05 were shown in bold.
[a]Continuous variables are shown in median [interquartile range]. Chi-square test for categorical variables and Mann-Whitney test for continuous variables.
[b]Including piggyback technique and side-to-side cavocavostomy.
BMI, body mass index; FFP, fresh frozen plasma; MELD, model for end-stage liver disease; PRBC, packed red blood cell.

Among the 14 factors included in the initial univariable model, 3 variables (MELD score, Karnofsky score, and Transfusion) were correlated each other. Donor type was correlated to hepatic vein reconstruction, and WIT was correlated to operative time. More than 1 multivariable models were identified; 1 with 4 covariates (donor type, MELD score, anhepatic time, and encephalopathy) retained in the model with goodness of fit (C-index = 0.73) (model 1); another model with 2 covariates (transfusion and anhepatic time) retained with C-index as 0.77 (model 2). Model 1 showed MELD score of 21–30 (OR, 0.49; 95% CI, 0.25-0.95; $P = 0.03$) and >30 (OR, 0.28; 95% CI, 0.10-0.78; $P = 0.02$) (ref. MELD score of 20 or lower), presence of encephalopathy (OR, 0.50; 95% CI, 0.27-0.95; $P = 0.04$), and anhepatic time >75 minutes (OR, 0.38; 95% CI, 0.21-0.69; $P = 0.001$) were less likely to undergo immediate extubation. Liver donor LT compared with donation after neurological determination of death donor LT was more likely to undergo immediate extubation (OR, 3.04; 95% CI, 1.15-8.06; $P = 0.03$). Model 2 showed the patients with anhepatic time >75 minutes were less likely to undergo immediate extubation than those with time ≤75 minutes (OR, 0.48; 95% CI, 0.26-0.89; $P = 0.02$); patients with total intraoperative blood transfusion ≥12 units were less likely to undergo immediate extubation than those who were transfused <12 units (OR, 0.11; 95% CI, 0.05-0.21; $P < 0.001$) (Table 3).

Reintubation Incidence and Indications

Three of the 80 patients (3.8%) in the immediate extubation group required reintubation within 1 week following LT. None of these 80 patients were reintubated within 48 hours after extubation. Two patients developed respiratory distress, one due to aspiration on POD

TABLE 2.

Univariable analysis of predictive factors for immediate extubation within the entire study cohort

Factors		No. of patients with immediate extubation (%)	Univariable analysis		
			OR	95% CI	*P*
Recipient age	<60	44 of 137 (32.1)	Ref.		
	≥60	36 of 142 (25.3)	0.72	0.43-1.21	0.21
Recipient BMI	20–24.9	17 of 51 (13.7)	Ref.		
	25–29.9	31 of 97 (31.9)	0.94	0.46-1.93	0.87
	30 or higher	31 of 94 (33.0)	0.66	0.32-1.34	0.25
Hepatitis C	No	43 of 177 (24.3)	Ref		
	Yes	37 of 102 (36.3)	1.77	1.03-3.01	**0.03**
MELD Score	≤20	54 of 147 (36.7)	Ref.		
	21–30	21 of 92 (22.8)	0.51	0.28-0.92	0.03
	>30	5 of 35 (14.3)	0.25	0.09-0.67	**0.006**
Encephalopathy	Absent	30 of 73 (41.1)	Ref.		
	Present	50 of 206 (24.3)	0.46	0.26-0.81	**0.007**
Karnofsky	40%–100%	67 of 220 (30.5)	Ref.		
	10%–30%	6 of 41 (14.6)	0.39	0.16-0.98	**0.04**
Donor type	Donation after neurological determination of death	66 of 234 (19.8)	Ref.		
	DCD	2 of 21 (9.5)	0.24	0.06-1.06	0.12
	Living	12 of 22 (54.5)	3.06	1.26-7.41	**0.004**
Cold ischemia time	Continuous (per h)		0.76	0.64-0.90	**0.001**
	≤6 h	70 of 217 (32.3)	Ref.		
	6.1–8 h	9 of 52 (17.3)	0.44	0.20-0.95	**0.04**
	>8 h	1 of 10 (10)	0.23	0.03-1.88	0.17
Anhepatic time	Continuous (per min)		0.98	0.97-0.99	**0.02**
	≤75 min	47 of 124 (37.9)	Ref.		
	>75 min	30 of 133 (22.6)	0.48	0.28-0.82	**0.008**
Warm ischemia time	Continuous (per min)				
	≤30 min	21 of 64 (32.8)	Ref		
	>30 min	59 of 215 (27.4)	0.77	0.42-1.41	0.41
Total intraoperative PRBC, FFP, and autologous transfusion	Continuous (per unit)		0.88	0.84-0.92	**<0.001**
	<12 units	68 of 146 (46.6)	Ref.		
	≥12 units	11 of 132 (8.3)	0.10	0.05-0.21	**<0.001**
Operative time	Continuous (per h)		0.70	0.58-0.84	**<0.001**
	≤6 h	36 of 90 (40)	Ref.		
	6.1–8 h	36 of 126 (28.6)	0.60	0.34-1.06	0.08
	>8 h	8 of 63 (12.7)	0.22	0.09-0.51	**<0.001**
Intraoperative vasopressor	No or single vasopressor	34 of 90 (37.8)	Ref.		
	Multiple vasopressor	46 of 189 (24.3)	0.49	0.29-0.84	**0.011**
Hepatic vein reconstruction	IVC replacement	12 of 22 (54.5)	Ref.		
	IVC preservation[a]	68 of 256 (26.6)	0.3	0.12-0.73	**0.008**

P values <0.05 were shown in bold.
[a]Including piggyback technique and side-to-side cavocavostomy.
BMI, body mass index; CI, confidence interval; DCD, donation after circulatory death; FFP, fresh frozen plasma; IVC, inferior vena cava; MELD, model for end-stage liver disease; OR, odds ratio; PRBC, packed red blood cells.

5 and another due to pulmonary edema on POD 3. One patient required reintubation on POD 3 for an exploratory laparotomy. Ten of 199 patients (5.0%) in the delayed extubation group required reintubation within 1 week following LT. There was no difference in reintubation rates between the immediate and delayed extubation group ($P = 0.65$). Of these 10 patients, 6 developed respiratory distress due to the following reasons: severe pulmonary edema (n = 2), aspiration (n = 2), pneumonia (n = 1), and severe atelectasis due to pleural effusion (n = 1) (Table 4). Additional indications for reintubation included altered mental status (n = 2) and cardiovascular instability (n = 2).

Risk Factor Analysis for Pulmonary Complications

Possible risk factors for pulmonary complications were assessed using a logistic regression model. In the univariable model, immediate extubation significantly decreased the risk of pulmonary complications, whereas total amount of intraoperative transfusion of ≥12 units significantly increased the risk of pulmonary complications. On multivariable model, immediate extubation was considered

TABLE 3.

Multivariable analysis of predictive factors for immediate extubation within the entire study cohort

		Model 1			Model 2		
		OR	95% CI	*P*	OR	95% CI	*P*
Anhepatic time	≤75 min	Ref.			Ref.		
	>75 min	0.38	0.21-0.69	**0.001**	0.48	0.26-0.89	**0.02**
Donor type	Donation after neurological determination of death	Ref.			–	–	–
	DCD	0.21	0.45-1.01	0.051	–	–	–
	Living donor	3.04	1.15-8.06	**0.03**	–	–	–
MELD score	≤20	Ref.			–	–	–
	21–30	0.49	0.25-0.95	**0.03**	–	–	–
	>30	0.28	0.10-0.78	**0.02**	–	–	–
Encephalopathy	Absence	Ref.			–	–	–
	Presence	0.50	0.27-0.95	**0.04**	–	–	–
Total intraoperative PRBC, FFP and autologous transfusion	<12 units	–	–	–	Ref.		
	≥12 units	–	–	–	0.11	0.05-0.21	**<0.001**

P values <0.05 were shown in bold.
CI, confidence interval; DCD, donation after circulatory death; FFP, fresh frozen plasma; MELD, model for end-stage liver disease; OR, odds ratio; PRBC, packed red blood cells.

as an independent factor associated with decreased risk of pulmonary complications after LT (OR, 0.34; 95% CI, 0.15-0.77; *P* = 0.01) (Table 5).

Comparisons of Posttransplant Outcomes

Posttransplant outcomes were compared in the entire group. The immediate extubation group had significantly lower ICU cost (US$5971 versus US$8524; *P* = 0.002), shorter ICU stay (2 d versus 3 d; *P* = 0.004), and lower pulmonary complication rate (12.5% versus 29.1%; *P* = 0.003) (Table 6).

These 2 groups were matched using an exact matched control method. A total of 144 patients, 72 in the immediate extubation group and 72 in the delayed extubation group, were selected (1 to 1 matching). Recipient, donor, and operative characteristics were similar between groups, except for anhepatic time (Table 7). Posttransplant outcomes in the matched groups were compared. Pulmonary complications were found to be significantly reduced in the immediate extubation group (11.1% versus 27.8%; *P* = 0.012). Number of ICU days was less in the immediate extubation group (2 d) compared with the delayed groups (3 d) (*P* = 0.082), whereas total number of hospital days was the same among the groups (*P* = 0.85). The median ICU cost for the immediate extubation group was lower than the delayed extubation group (US$5700 and US$7710), but the difference was not statistically significant (*P* = 0.11)

TABLE 4.

Reintubation indications amongst delayed and immediate extubation groups after liver transplantation

Reintubation indication	Delayed extubation (n = 10)	Immediate extubation (n = 3)
Respiratory distress/hypoxia	6	2
Altered mental status	2	–
Reoperation	–	1
Cardiovascular instability	2	–

(Table 8). Graft survival at 90 days, reintubation rates, and readmission within 30 days were not different among the groups.

DISCUSSION

In our study, we attempted to identify predictors for immediate extubation in LT patients and further examine how this practice impacts patient outcomes. After risk adjustment, anhepatic time of >75 minutes, total amount of intraoperative transfusion of ≥12 units, presence of encephalopathy, and higher MELD score were associated with decreased likelihood of immediate extubation after LT. Living donor LT, compared with LT using liver grafts from donation after brain-death donors, showed significantly higher likelihood of immediate extubation. Shorter anhepatic time, less transfusion requirements, and shorter operative time may be markers of a straightforward surgery, which may be more likely be associated with immediate extubation. It has been reported that anhepatic time of >100 minutes has been associated with increased incidence of graft dysfunction.[11] The accumulation of metabolic byproducts normally dependent on hepatic clearance during this period increases substantially. Their subsequent release during reperfusion can cause deleterious hemodynamic effects, which may preclude immediate extubation. Biancofiore et al[12,13] reported that there was a significant association between amount of transfusion and immediate extubation. Blood loss is affected by difficulties in surgeries and liver graft function. It should be noted that the importance of liver graft function assessment in deciding immediate extubation was emphasized by 2 separate groups.[4,13] One of the novel findings from our study is the association between anhepatic time and immediate extubation. Shortening anhepatic time may decrease the risk of liver graft dysfunction, potentially leading to less blood loss and transfusion, which may lead to increased likelihood of immediate extubation.[11]

MELD score is considered an objective measure of severity of illness, whereas it remains controversial if

TABLE 5.

Risk factor analysis for pulmonary complications within the entire study cohort

Factors		Univariable analysis			Multivariable analysis[a]		
		OR	95% CI	*P*	OR	95% CI	*P*
Immediate extubation (Ref. delayed)		0.35	0.17-0.72	**0.005**	0.34	0.15-0.77	**0.01**
Recipient age ≥60 y (Ref. <60 y)		1.30	0.75-2.26	0.345			
Recipient sex	Male	0.72	0.41-1.27	0.26			
Recipient ethnicity	Caucasian	Ref.					
	African American	1.60	0.69-3.72	0.28	1.74	0.73-4.16	0.214
	Others	2.84	1.07-7.57	**0.037**	2.51	0.90-6.97	0.078
Recipient BMI	20–24.9	Ref.					
	25–29.9	1.45	0.62-3.42	0.396			
	30 or higher	1.88	0.83-4.28	0.128			
MELD Score	≤20	Ref.					
	21–30	1.09	0.60-1.98	0.782			
	>30	0.77	0.33-1.82	0.554			
Encephalopathy	None	Ref.					
	Grade 1 or 2	1.06	0.56-2.01	0.863			
	Grade 3 or 4	1.28	0.46-3.58	0.637			
Karnofsky 10%–30% (Ref. 40%–100%)		0.84	0.38-1.88	0.677			
Donor type	Donation after neurological determination of death	Ref.					
	DCD	1.78	0.72-4.42	0.22			
	Living	1.25	0.47-3.35	0.66			
Donor age	<40	Ref.					
	40–59	0.92	0.50-1.69	0.792			
	≥60	1.55	0.72-3.37	0.265			
Donor sex	Male	1.34	0.78-2.33	0.291			
Donor BMI	20–24.9	Ref.					
	25–29.9	1.15	0.55-2.39	0.717			
	30 or higher	0.98	0.47-2.07	0.962			
	<20	1.72	0.56-5.31	0.346			
Donor ethnicity	Caucasian	Ref.					
	African American	1.12	0.53-2.39	0.761			
	Others	1.06	0.28-4.04	0.937			
Cold ischemia time	≤6 h	Ref.					
	6.1–8 h	1.03	0.54-1.94	0.935			
	>8 h	1.21	0.58-2.55	0.607			
Warm ischemia time >30 min (Ref. ≤30 min)		0.63	0.34-1.17	0.146			
Anhepatic time >75 min (Ref. ≤75 min)		0.68	0.38-1.20	0.183			
Total intraoperative PRBC, FFP, and autologous transfusion ≥12 units (Ref. <12 units)		1.77	1.01-3.08	**0.045**	1.18	0.63-2.20	0.607
Operative time	≤6 h	Ref.					
	6.1–8 h	1.03	0.54-1.94	0.935			
	>8 h	1.21	0.58-2.55	0.607			
Intraoperative multiple vasopressor (Ref. No. or single vasopressor)		0.87	0.49-1.55	0.639			

P values <0.05 were shown in bold.

[a]Significant factors on univariable analysis were included.

BMI, body mass index; CI, confidence interval; DCD, donation after circulatory death; FFP, fresh frozen plasma; MELD, model for end-stage liver disease; OR, odds ratio; PRBC, packed red blood cells.

MELD score can be utilized as one of the criteria for immediate extubation. Other groups found little impact of MELD score on successful extubation.[12] A group from Colorado applied "universal intent to treat" for immediate extubation.[4] Our results showed an independent association between MELD score and immediate extubation. It may be important to comprehensively assess these patient factors when deciding indications of immediate extubation, because background of severity of illness may be multifactorial.

Presence of hepatic encephalopathy can present 2 issues for extubation.[14-16] Altered mental status can prohibit extubation, especially if the patient cannot demonstrate the ability to protect their airway. Second, hepatic encephalopathy is a clinical manifestation of decompensated liver function, which means other characteristics of liver failure

TABLE 6.

Outcome measures within the entire 279 patients

	Extubation timing		
Outcome measure	Delayed extubation (n = 199)	Immediate extubation (n = 80)	*P*
ICU costs, USD [IQR]	8524 [5019, 16887]	5971 [1287, 13648]	**0.002**
ICU stay, d [IQR]	3 [2, 5]	2 [1, 4]	**0.004**
Hospital stay, d [IQR]	9 [7, 16]	9 [6, 13.75]	0.08
Reintubation within 1 wk, N (%)	10 (5)	3 (3.8)	0.65
Pulmonary complications < 3 mo, N (%)	58 (29.1)	10 (12.5)	**0.003**
Severe/moderate	26 (13.1)	7 (8.8)	
Mild	32 (16.0)	3 (3.7)	
Readmission <1 mo, N (%)	57 (28.6)	21 (26.3)	0.45
Graft survival at 90 d	95.5%	96.3%	0.32

P values <0.05 were shown in bold.
ICU, intensive care unit; IQR, interquartile range.

may be present, and together these factors may play a synergistic role in requiring prolonged mechanical ventilation especially if there is delayed graft function. One patient who was immediately extubated required reintubation on POD 5 due to aspiration and altered mental status. This patient had grade 3 encephalopathy at the time of LT. Overall, our decisions on immediate extubation were successful, because no patients required reintubation in the operating room, on arrival to the ICU, or even within 48 hours after extubation. However, careful assessment of a patient's mental status is critical, especially when encephalopathy is evident pre-LT.

Living donor LT showed a significantly higher likelihood of immediate extubation, which remained as an independent predictive factor. Reasons for this finding may be multifactorial. Living donor LT recipients may be less sick, represented by lower MELD score, have less encephalopathy, and have shorter CIT (data not shown), all of which might be attributable to the higher likelihood of immediate extubation in this population. DCD LT has been suggested to have inferior outcomes as compared with donation after brain-death donors possibly due to hypoxia and hypotension during the agonal phase of donor; however, this finding is not consistent among centers.[17-19] During this time period, accumulation of inflammatory cytokines, which directly damage the donor organ, will also be released within the recipient's circulation during reperfusion and can cause hemodynamic and cardiovascular instability.[20,21] Our study did not show significant association between DCD LT and immediate extubation, compared with those who received donation after neurological determination of death donors. These results may indicate that donor type should not preclude immediate extubation. Instead, it would be important to assess liver graft function, such as improvement in coagulopathy and lactate clearance.

According to the univariable analysis, other factors which were associated with decreased likelihood of immediate extubation included hepatitis C, lower Karnofsky score (10%–30%), prolonged CIT (>8 h), prolonged operative time (>8 h), IVC preservation as hepatic vein reconstruction (piggyback technique, cavocavostomy technique), and multiple vasopressor requirement during LT surgery. None of these factors remained as an independent factor after risk adjustment. It should be noted that careful interpretations on the results of the multivariable analysis are necessary because of the small sample size. It was reported that patients who had a higher severity of illness, prolonged surgery time, and intraoperative hemodynamic instability showed lower likelihood of immediate extubation.[13]

We preferentially used the piggyback technique for the hepatic vein reconstruction. The IVC replacement technique was used only in 7.9%. Although our study showed that the IVC replacement technique (bicaval technique) increased likelihood of immediate extubation, this did not remain as an independent predictive factor. The IVC preservation group had significantly higher intraoperative transfusion requirements (11.5 units, IQR [5.0, 22.0]) versus 5.5 units, IQR [2.0, 10.0]) (data not shown). There might be confounding effects between the hepatic vein reconstruction techniques and intraoperative blood transfusion. Based on the multivariable analysis, intraoperative transfusion was considered as an independent predictive factor. Hence, it is difficult to draw a firm conclusion or recommendation on the association between the hepatic vein reconstruction techniques and immediate extubation.

Very little overlap with regards to predictive factors for immediate extubation, either positive or negative, exists within the literature.[14-17] Two limiting factors can be attributed to this. First, surgical technique, which can impact the donor graft function by way of ischemia time, varies across institutions. Second, there is a lack of uniformity of LT recipient demographics and clinical status. For example, several other studies reported an average MELD score of <15, whereas in our study cohort the average MELD score was 21 for the delayed extubation group and 17 for the immediate extubation group.[15,16]

At the time of our study period, there were no institutional guidelines in place for immediate extubation. The decision to extubate was based on a discussion between the surgeon and anesthesiologist. Standard extubation criteria including hemodynamic stability, adequate oxygenation and ventilation, reversal of neuromuscular blockade, ability to protect the airway, and factors specific to LT, including adequate graft function and minimal transfusion requirements, were taken into consideration. Decision process might cause heterogenicity of extubation criteria

TABLE 7.

Comparisons of characteristics between the matched groups

Factor		Timing of extubation: Delayed (in intensive care unit) N = 72	Timing of extubation: Immediate (in operating room) N = 72	*P*
Recipient age (%)	≥60 y	45 (62.5)	35 (48.6)	0.131
Recipient gender (%)	Male	48 (66.7)	49 (68.1)	>0.9
Recipient ethnicity (%)	White	55 (76.4)	61 (84.7)	0.432
	Black	11 (15.3)	8 (11.1)	
	Others	6 (8.3)	3 (4.2)	
Hepatitis C (%)		26 (36.1)	33 (45.8)	0.309
Hepatocellular carcinoma (%)		29 (40.3)	28 (38.9)	>0.9
Recipient BMI (%)	20–24.9	14 (19.7)	13 (18.3)	0.72
	25–29.9	28 (39.4)	29 (40.8)	
	≥30	27 (38.0)	29 (40.8)	
	<20	2 (2.8)	0 (0.0)	
MELD score	≤20	51 (70.8)	48 (66.7)	0.775
	21–30	18 (25.0)	19 (26.4)	
	>30	3 (4.2)	5 (6.9)	
Encephalopathy	Present	44 (61.1)	44 (61.1)	>0.9
Karnofsky score (%)	10%–30%	5 (6.9)	6 (8.3)	>0.9
Donor type (%)	Donation after neurological determination of death	59 (81.9)	59 (81.9)	0.445
	DCD	5 (6.9)	2 (2.8)	
	Living donor	8 (11.1)	11 (15.3)	
Donor age (%)	≤40	30 (41.7)	34 (47.2)	0.749
	41–60	31 (43.1)	27 (37.5)	
	>60	11 (15.3)	11 (15.3)	
Donor gender (%)	Male	41 (56.9)	42 (58.3)	>0.9
Donor BMI (%)	20–24.9	21 (30.9)	17 (23.6)	0.283
	25–29.9	23 (33.8)	24 (33.3)	
	≥30	23 (33.8)	25 (34.7)	
	<20	1 (1.5)	6 (8.3)	
Donor ethnicity (%)	White	59 (81.9)	57 (79.2)	0.778
	Black	10 (13.9)	13 (18.1)	
	Others	3 (4.2)	2 (2.8)	
Cold ischemia time (%)	≤6 h	63 (87.5)	64 (88.9)	>0.9
	6.1–8 h	8 (11.1)	7 (9.7)	
	>8 h	1 (1.4)	1 (1.4)	
Warm ischemia time (%)	≥30 min	52 (72.2)	52 (72.2)	>0.9
Anhepatic time (%)	≥75 min	38 (58.5)	27 (39.1)	**0.038**
Total amount of intraoperative transfusion (PRBC, FFP, autologous) (%)	≥12 units	16 (22.2)	10 (13.9)	0.279

P values <0.05 were shown in bold.
BMI, body mass index; DCD, donation after circulatory death; FFP, fresh frozen plasma; MELD, model for end-stage liver disease; PRBC, packed red blood cell.

among teams, whereas the variety of patient and operative characteristics in this study cohort allowed us to identify several factors, which can be attributed to immediate extubation. According to the findings of this study, our institution has come up with guidelines for providers to take into consideration when determining if their patient is a potential candidate for immediate extubation (Table 9). It should be noted that these criteria would provide guidance to anesthesia and surgery teams when deciding if a patient should undergo immediate extubation; we acknowledge that patients who do not meet all of criteria could be extubated in the operating room after LT. The utility of such guidelines could be examined in future studies.

It is also important to acknowledge that there is a learning curve as new practices are introduced. Within our study, we did not compare the incidence of immediate extubation across each year or the incidence of extubation by anesthesia providers. In the earlier years of our study period, there may have been more patients eligible for immediate extubation but did not undergo immediate extubation secondary to provider unfamiliarity. To address this concern, we used exact matched case controls to assess clinics effects of immediate extubation on their posttransplant course. Severity of illness, surgical factors, and donor factors were well balanced between the matched groups.

TABLE 8.

Outcome measures between the matched groups

	Timing of extubation		
Outcome measure	Delayed (n = 72)	Immediate (n = 72)	*P*
ICU costs, USD [IQR]	7710 [4840, 12453]	5700 [1287, 13392]	0.11
ICU stay, d [IQR]	3 [2, 4]	2 [1, 4]	0.082
Hospital stay, d [IQR]	8.5 [6.8-12]	9 [6, 13.25]	0.85
Reintubation within 1 wk, N (%)	2 (2.8)	2 (2.8)	>0.9
Pulmonary complications <3 mo, N (%)	20 (27.8)	8 (11.1)	**0.012**
Severe/moderate	7 (9.7)	2 (2.8)	
Mild	13 (18.1)	6 (8.3)	
Readmission <1 mo, N (%)	18 (25.0)	21 (29.2)	0.29
Graft survival at 90 d	98.6%	95.8%	0.31

P values <0.05 were shown in bold.
ICU, intensive care unit; IQR, interquartile range.

How the practice of immediate extubation post-LT impacts clinical outcomes was looked at within our entire study cohort and the matched case-control cohort. Delayed extubation, as mentioned previously, may be attributed to several factors including underlying severity of illness and complexity of surgery. Better outcome measures within the immediate extubation group could therefore be associated with less sick patients and a more straightforward surgery, not the act of immediate extubation itself. This is a limitation of previous studies, which attempted to assess how immediate extubation post-LT impacts outcomes.[4,13,14] To address this concern in our study, donor, and operative characteristics were matched between groups and outcomes were compared. To our knowledge, this is the only study that uses matched case controls to look at postoperative complications and benefits following immediate extubation post-LT. By using matched case controls, we showed patients who underwent immediate postoperative extubation were not at increased risk for reintubation and that these patients had decreased incidence of pulmonary complications. ICU cost and length of stay were also subsequently less in the immediate extubation group. Reversed sedation for immediate extubation might affect pain perception, which may decrease the risk of pulmonary complications.[22] This may account for the lower risk of pulmonary complications in those who underwent immediate extubation.

TABLE 9.

Institutional guidelines for immediate extubation

Patient factors
- PaO_2/FiO_2 ratio >200
- No moderate or severe encephalopathy (grade 3 or 4) in the immediate preoperative period
- No hepatopulmonary syndrome or portopulmonary hypertension
- MELD score <30

Surgery factors:
- <12 units of transfused blood products
- Surgery time <8 h
- None or single vasopressor at the end of surgery
  - Minimal vasopressor requirement (vasopressin 2 U/h or less or norepinephrine 5 mcg/min or less)

Intraoperative assessment
- Adequate graft function (lactate clearance, improving acidosis, improving coagulation profile)
- Resolution of coagulopathy at the time of incision closure

MELD, model for end-stage liver disease.

Given the safety and potential benefits of immediate extubation, immediate extubation should be considered in appropriate candidates. We recommend these patients still be closely monitored in the immediate postoperative period secondary to the possible need for reintubation. Some centers have described their practice of bypassing the ICU for LT patients who were immediately extubated and instead admitting them to a transplant specific floor with close monitoring.[9,10] Within the immediate extubation group, there may be patients who are at significantly lower risk for reintubation who would be appropriate candidates for this practice. In our study, we only focused on the indication for reintubation within 1 week, not the progression and risk factors that led to the event. By identifying low risk patients, we could reduce ICU stay and cost without sacrificing care and safety.

Limitations of this study should be stated. First, we acknowledge that the numbers of patients and primary outcome (immediate extubation) evaluated in this study were small. To preserve the stability of the multivariable model, we had to limit the number of variables in the final model. We selected 14 variables for the initial univariable model. We assessed correlation among those 14 factors and eventually restricted the maximum number to 8 variables to be included in the first multivariable model. We used backward model selection. Two final multivariable models were created using the retained covariates. However, this method might miss including variables in the model that may have an important association with immediate extubation. Therefore, the results of this multivariable analysis should be interpreted cautiously. Future studies need be conducted with the larger sample size. Second, this study did not investigate the roles of postextubation strategies such as high-flow nasal cannula and noninvasive positive pressure ventilation for the purpose of prevention of respiratory distress after extubation. These strategies may increase likelihood of immediate extubation and change the predictive factors for immediate extubation.

In conclusion, the applicability of our findings across institutions is difficult as this was a single-center study, and patient demographics, surgical technique, and anesthetic management vary across transplant institutions. However, we were able to show the practice of immediate extubation is associated with a lower risk of pulmonary complication and reduced ICU stay and cost. Given the benefits of immediate extubation in LT patients, immediate (rather than delayed extubation) should be considered when appropriate. Identifying predictive factors of immediate extubation continues to be a challenge across institutions; however, institutions are able to identify predictive factors within their centers that can impact their practice. The continued surgical and anesthetic advancement in LT may make it feasible to bypass the ICU with certain patients and improve hospital resource allocations.

ACKNOWLEDGMENTS

Authors thank Dr Mei Lu, PhD, Henry Ford Health System, for her participation in the statistical analysis.

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