

ORIGINAL INVESTIGATION

Predictors of success of immediate tracheal extubation in living donor liver transplantation recipients[☆]



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Abstract

Background: Early tracheal extubation of recipients following liver transplantation (LT) has been gradually replacing the standard postoperative prolonged mechanical ventilation, contributing to better patient and graft survival and reduced costs. There are no universally accepted predictors of the success of immediate extubation in LT recipients. We hypothesized several potential predictors of successful immediate tracheal extubation in living donor liver transplantation (LDLT) recipients.

Aim: Evaluation of the validity of the following hypothesized factors: model for end-stage liver disease (MELD) score, duration of surgery, number of intraoperatively transfused packed red blood cells (RBCs) units, and end of surgery (EOS) serum lactate, as predictors of success of immediate tracheal extubation in living donor liver transplantation (LDLT) recipients.

Methods: In this prospective clinical investigation, perioperative data of adult living donor liver transplantation (LDLT) recipients were recorded. “Immediate extubation” was defined as tracheal extubation immediately and up to 1 hour post-transplant in the operating room. Patients were divided into the extubated group who were successfully extubated with no need for reintubation, and the non-extubated group who failed to meet the criteria of extubation, or were re-intubated within 4 hours of extubation.

Results: We enrolled 64 patients candidates for LDLT; 50 patients (76.9%) in group 1 were extubated early after LDLT while 14 patients (23.07%) in group 2 were transferred to the intensive care unit intubated. After data analysis, we found that EOS serum lactate, duration of surgery and number of packed RBCs units transfused intraoperatively were good predictors of success of immediate extubation ($p < 0.001$). MELD scores did not show any significant impact on the results ($p = 0.54$). Other factors such as EOS urine output and blood gases indices were shown to have a significant effect on the decision of extubation ($p = 0.03$ and 0.006 , respectively).

[☆] Study conducted at Ain Shams University Specialized Hospital, Ain Shams University, Cairo, Egypt.

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Conclusions: EOS serum lactate, duration of surgery and number of packed RBCs units transfused were potential predictors of post-transplant early extubation.

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Introduction

Orthotopic liver transplantation (LT) is the definitive treatment for acute liver failure, end-stage liver disease (ESLD), advanced liver cirrhosis, and liver tumors.¹ In our center we previously encouraged that leaving the patient sedated on mechanical ventilation is the standard care following LT. Clinicians believe that this type of clinical management improves outcomes by providing a smooth transition to the recovery phase and reducing physiological stress caused by awakening and spontaneous ventilation. This had remained the common practice despite the lack of evidence that routine postoperative ventilation or intensive care unit (ICU) admission prevents perioperative complications or benefits donor organ function.² Developments in the preoperative assessment, surgical techniques, and postoperative care made immediate extubation following LT a feasible and safe procedure for a significant number of patients.³ Immediate extubation in LT recipients was reported in the early 1990s. Nowadays, early extubation after LT has been successful in many patients and is gradually being adopted in more and more hospitals.⁴

However, the determination of the appropriate tracheal extubation timing and conditions remains important in securing safe and reasonable patient recovery after LT. No definitive or universal criteria have yet been established regarding the predictors of early tracheal extubation in LT patients.⁵ Although immediate extubation variables are the same as those for any other surgery, it is a complex decision for patients who have undergone LT, and there is a learning curve, as it can take some time to increase the immediate extubation success rate.³

In 2014, Lee and colleagues demonstrated that several factors, including model for end-stage liver disease (MELD) score, lung disease, encephalopathy, ascites, surgical time, transfusion of packed red blood cells (RBCs), urine output, vasopressors, and serum lactate all may affect the decision of early extubation. However, after multivariate analysis, only packed RBC transfusion and end-of-surgery (EOS) serum lactate were selected as predictors of early extubation after living donor liver transplantation (LDLT).⁵ Elnour and Milan,³ reviewed 32 controlled trials on early extubation following LT, and listed factors affecting early extubation, which included: primary liver disease, age, gender, body mass index (BMI), comorbidities, MELD score, encephalopathy, previous abdominal surgery, graft function, duration of anhepatic phase, amount of intraoperative blood replacement, duration of surgery, inotropes at the end of the surgery, lactate at the end of surgery, and temperature. They mentioned factors that were not considered because they were not easily measurable, but may have a significant impact, such as the medical centers' experience, the quality of teamwork, local protocols, and supporting services,

such as nutritionists, social workers, physiotherapists, and recovery room/high dependency unit/ICU settings, therefore mentioning that clinical judgment remains an important factor in decision-making.³

Based on previous clinical experience at our center and relevant publications, we aimed to investigate potential predictors of successful immediate tracheal extubation in LDLT recipients, including MELD score, length of surgery, the number of units of packed RBCs transfused intraoperatively, and EOS serum lactate.

Methods

The academic and ethical committee of the faculty of medicine, Ain-Shams University, approved the study with approval no. FMASU MD 92/2017. The total sample size was 64 patients. All patients enrolled in this study were recipients of LDLT admitted to Ain Shams Center for Organ Transplant (ASCOT). Written informed consent was obtained from every patient or legal guardian after having explained the procedure.

Type of the study

Prospective observational clinical investigation on recipients of living donor liver transplantation. Adult patients aged 18–60 years, of both sexes, with ESLD scheduled to receive LDLT. Exclusion criteria were emergency transplant, encephalopathy at the time of surgery, re-transplant and the presence of major intraoperative surgical complications such as massive bleeding and injury of major vascular structures or diaphragm.

Anesthetic technique

Preoperative assessment and preparation were performed according to the institutional protocol. General anesthesia was started with a modified rapid sequence induction. Intraoperative monitoring included: 5-lead ECG, invasive arterial blood pressure, noninvasive blood pressure, continuous central venous pressure (CVP), body temperature, oxygen saturation (SaO₂), capnometry (EtCO₂), and urine output (mL). Anesthesia was maintained with a balanced anesthetic technique, consisting of a volatile agent (Isoflurane or Sevoflurane) and a mixture of air and oxygen (FiO₂ 0.5), atracurium infusion at a dose of 0.25 mg.kg⁻¹.h⁻¹ and fentanyl infusion at a dose of 1–2 mcg.kg⁻¹.h⁻¹. Patients were mechanically ventilated, with ventilator parameters adjusted to achieve normocarbida with an inclination to hyperventilation and hypocapnia during the anhepatic phase to correct metabolic acidosis without resorting to chemical buffers such as sodium bicarbonate.

At the end of the surgery, all patients were prepared for the emergence and tracheal extubation. Fentanyl and atracurium infusions were discontinued 45 minutes before the expected time of extubation. The inhaled anesthetic was stopped at the beginning of skin closure, when patients were awake and able to follow commands and regaining full muscle strength (neuromuscular monitoring: train of four more than 1/4 was satisfactory for extubation). Additionally, the usual criteria for extubation was adopted, including hemodynamic stability with no or minimal vasopressor support (noradrenaline $< 0.1 \text{ mcg.kg}^{-1}.\text{min}^{-1}$), normothermia (temperature $> 36 \text{ }^{\circ}\text{C}$), a positive gag response, spontaneous breathing with sufficient tidal volume ($5\text{--}8 \text{ mL.kg}^{-1}$), and respiratory rate of less than 20 breaths/min, normocarbica (evaluated by end-tidal carbon dioxide analysis), and satisfactory arterial blood gas analysis (ABG). pH less than 7.2 PO_2 less than 80 mmHg and PCO_2 more than 45 mmHg were against trials of extubation.³ In the event of fulfilling all the criteria, endotracheal and oral suctioning was done, followed by extubation. Oxygen therapy was started in the form of an oxygen mask or nasal prongs. Patients were monitored for any sign of respiratory distress, desaturation, or disturbed consciousness level that may require reintubation. Failure of immediate extubation included patients who did not meet the stated criteria and those who were reintubated within 4 hours after extubation. Thirty minutes following skin closure was considered a time limit for failure of extubation and no further trials of extubation were performed in the operation theatre.

Measurements

Intraoperatively: Serum lactate (mmol.L^{-1}) and pH from arterial blood gas (ABG) analysis were rerecorded immediately at four different timings; T1, after insertion of an arterial cannula, T2, during the anhepatic phase, T3, 30 minutes after reperfusion, T4, at the end of surgery (EOS). Blood product requirements were recorded as the number of units of packed RBCs transfused intraoperatively. Duration of surgery (hours) calculated from induction of anesthesia until the end of skin suturing. Vital data at the end of surgery such as mean arterial blood pressure (MABP) (mmHg), heart rate (HR) (beats/min, BPM), body temperature ($^{\circ}\text{Celsius}$), hemodynamic support at the end of surgery Noradrenaline ($\mu\text{g.kg}^{-1}.\text{min}^{-1}$), urine output (UOP) (mL.h^{-1}) recorded during the last hour of surgery before recovery.

Endpoints

The primary endpoint was the success of immediate extubation with no need for reintubation within 4 hours after extubation.

Statistical methods

The statistical analysis was performed using a standard SPSS software package version 22 (SPSS Inc., Chicago, IL, USA). Normally distributed numerical data are presented as mean \pm SD, and differences between groups were compared using the independent Student's *t*-test. Data not normally

distributed were compared using the Mann-Whitney test and are presented as median (IQR). Categorical variables were analyzed using the χ^2 test or Fisher's exact test and are presented as number (%). The odds ratio was used to assess the predictors for extubation. All *p*-values are two-sided < 0.05 is considered statistically significant. The sensitivity and specificity of possible predictors were evaluated by the area under the receiver operating characteristic (ROC) curve (AUC).

Results

We enrolled 64 ESLD patients' candidates for living donor liver transplantation; demographic data were recorded and compared for patients of both extubated and the non-extubated groups (Table 1). There was a significant difference between the two study groups ($p = 0.013$) concerning the pathology of ESLD.

Preoperative MELD scores showed no statistical difference ($p = 0.54$) in the decision of extubation of the patients.

Of the total sample size of 64 patients, 50 patients (76.9 %) met the criteria for successful extubation with no need for reintubation within 4 hours of extubation: Extubated group. On the other hand, 14 patients (23.1 %) did not meet the extubation criteria and so remained intubated after the operation and were transferred to the ICU with their endotracheal tubes in place: Non-extubated group.

At the end of surgery all 64 patients were assessed for the possibility of extubation, and evaluated for possible predictors for extubation. Fifty patients (76.9 %) were extubated successfully, no patients (0%) required re-intubation within the first 4 hours, 14 patients (23.1 %) were not extubated; 5 patients from both groups (7.6%) developed postoperative respiratory complications in the form of Pneumonia ($n = 3$), lung collapse ($n = 2$) all these patients were among the non-extubated group.

Higher EOS serum lactate was found among the non-extubated group of patients (11.4 ± 3.49) when compared to the extubated group (5.39 ± 2.9) ($p < 0.001$). Lactate measured 30 minutes after reperfusion was also reduced ($p = 0.014$) but to a lesser extent than at the end of surgery. On the other hand, when comparing the two groups as regards lactate measured after induction and during the anhepatic phase, no difference was detected ($p = 0.34$ and 0.94 respectively) (Table 2). There was a difference when comparing both groups in regard to pH during the an-hepatic phase ($p = 0.001$) and also at the end of surgery ($p = 0.006$). There was also a high statistical difference between groups 30 minutes after reperfusion ($p < 0.001$) (Table 2).

As noted in Table 2, Patients of the non-extubated group received higher amounts of blood products ($p = 0.004$). Duration of surgery was found to be longer in the non extubated group (11.6 ± 2.67 hrs) than in the extubated group (9.74 ± 1.35) ($p = 0.056$) with Odd's ratio 0.611. Hemodynamic support (defined by high doses of norepinephrine) is lower in the extubated group 0 ($0\text{--}0.05$) microgram. $\text{kg}^{-1}.\text{min}^{-1}$, than in the non extubated group 0.065 ($0.02\text{--}0.14$) microgram. $\text{kg}^{-1}.\text{min}^{-1}$ ($p = 0.001$).

EOS urine output in mL.h^{-1} showed higher values among the extubated group ($p = 0.03$) especially during the last hour of the operation ($231.8 \pm 75.43 \text{ mL.h}^{-1}$).

Table 1 Comparing the extubated and non-extubated groups regarding age, sex, Body mass index (BMI), diagnosis, and Child-Pugh class.

	Extubated		Non extubated		p-value
Age (years, mean ± SD)	48.88 ± 8.92		46.67 ± 11.04		0.11
Sex	Male	Female	Male	Female	0.377
	27	23	9	5	
BMI (kg.m ⁻²)	28.33 ± 3.04		27.04 ± 4.64		0.21
Diagnosis -ESLD, HCV	24		3		0.013*
-ESLD, HCV, HCC	3		3		
-ESLD, HBV	8		0		
-ESLD, HCV, Previous HBV	3		1		
Child-Pugh class					0.258
-C	27		7		
-B	23		7		
MELD Score	17 (13-21)		16 (14-19)		0.54

ESLD, End stage liver disease; HCV, Hepatitis C virus; HCC, Hepatocellular carcinoma; HBV, Hepatitis B virus; MELD, Model for end stage liver disease.

$p < 0.05$ is considered statistically significant.

Table 2 Comparing the extubated and non-extubated groups with respect to serum lactate, pH packed RBCs transfused at different intraoperative stages.

Serum lactate (mmol.L ⁻¹)	Extubated (n = 50)	Non-extubated (n = 14)	p-value
Baseline	1.24 ± 0.54	1.35 ± 0.46	0.34
Anhepatic	4.8 ± 1.92	4.84 ± 2.5	0.94
30 min after reperfusion	5.5 ± 2.31	7.4 ± 3.3	0.014*
EOS	5.39 ± 2.9	11.4 ± 3.49	< 0.001**
PH	Extubated (n = 50)	Non-extubated (n = 14)	p-value
Baseline	7.42 ± 0.05	7.43 ± 0.056	0.32
Anhepatic	7.33 ± 0.08	7.2 ± 0.11	0.001*
30 min after reperfusion	7.27 ± 0.07	7.18 ± 0.127	< 0.001**
EOS	7.3 ± 0.89	7.24 ± 0.08	0.006*
Number of packed PRBCs	Extubated	Non-extubated	
No. of units	1 (0–2)	3 (2–4)	0.004*

EOS, end of surgery.

Data are presented as mean ± SD.

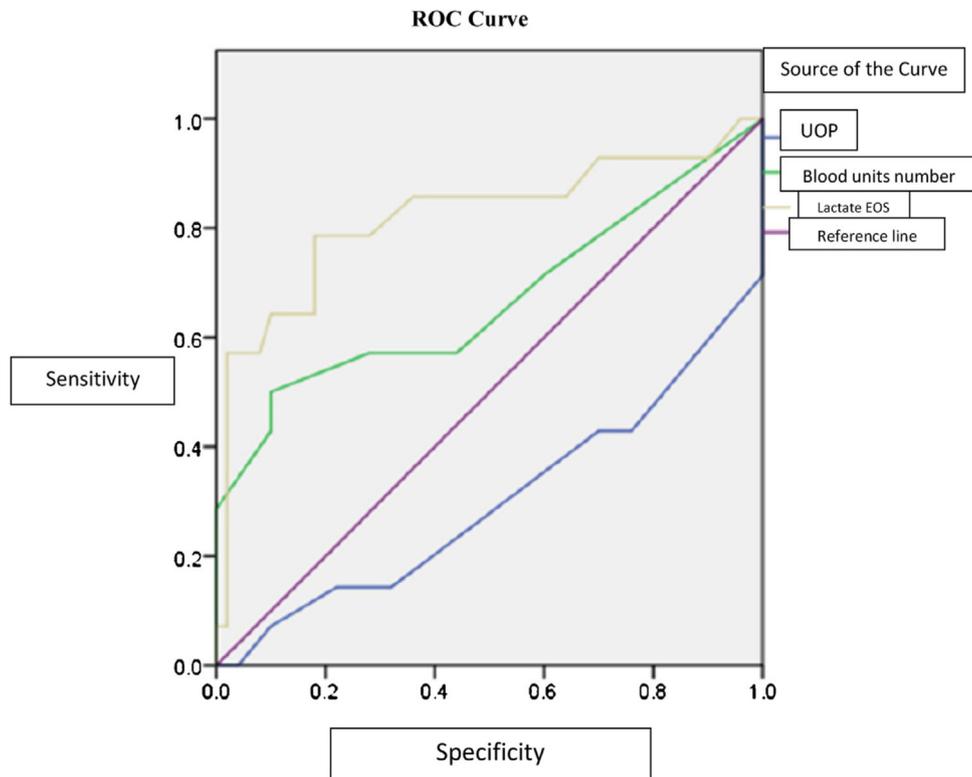
$p < 0.05$ is considered statistically significant.

Values shown to have high significance were chosen as common indicators for early extubation. These included blood products, UOP and EOS serum lactate. They were represented in the ROC curve to show their sensitivity and specificity as follows in [Figure 1](#).

Discussion

The definition of “Early” extubation following LT is tracheal extubation immediately or within 1 hour post-transplant in the operating room.⁷ If a patient who undergoes early post-transplant extubation is transferred directly to a surgical ward without an ICU stay, the expression “fast-tracking” may be used in place of early extubation. Early extubation

is an essential component of fast-tracking, and the patient undergoes major recovery in the post anesthesia care unit.⁵ Most studies about fast-tracking have discussed the pros and cons of fast-tracking. However, limited studies have been performed on how and when to extubate a patient who has undergone LT in the operating theatre, and which factors affect the decision-making process.³ The current study was conducted on a total of 64 adult patients aged 18–60 years, of both sexes, with ESLD. All of which were candidate recipients of living donor liver transplantation admitted to Ain Shams Center for Organ Transplant (ASCOT). Of the 64 patients, 50 patients (76.9 %) were successfully extubated, while 14 (23.1 %) patients remained intubated postoperatively.



	AUC	Sensitivity	Specificity
UOP	0.301	71.4%	36%
Blood transfusion	0.669	30%	100%
EOS Serum lactate	0.821	85.7%	74.4%

UOP, urine output; EOS, end of surgery.

Figure 1 Receiver operating characteristic (ROC) curve of the two study groups. UOP, urine output; EOS, end of surgery.

When analyzing the proposed predictors of the success of immediate extubation, our study surprisingly showed no significant difference when comparing MELD between the extubated and non-extubated groups, indicating that MELD scores may not be an accurate predictor for early extubation after surgery. These results were supported in a remarkable case report by Li et al., of a 48-year-old male patient with ESLD secondary to Hepatitis B with a documented MELD score of 41 who was successfully extubated in the operating room at the end of LT surgery.⁸ Interestingly Lee and colleagues, while performing another study on 107 patients of which 66 were extubated early after LDLT, noticed the significant difference in the MELD score between patients who were successfully extubated (lower MELD score) and those who remained mechanically ventilated. However, after multivariate adjustment with intraoperative factors in their study, the role of MELD scores as a predictor of early tracheal extubation in LT has disappeared.⁵ In contrast to our study, Bulatao and colleagues, in a single-variable analysis found that successful fast-tracking was significantly more likely for patients with lower MELD scores.⁹ Similarly, in a prospective analysis of 354 patients by Biancofiore et al., a MELD score < 11 was reported to have predictive power for

identifying subjects with a higher likelihood of immediate extubation.⁶

In our study, baseline and anhepatic phase serum lactate levels showed no significant variation between the two groups, while when measured 30 minutes after reperfusion and at EOS, a highly statistically significant difference was demonstrated. Similar to our study, Elnour and Milan, in their review, concluded that EOS serum lactate is of high significance when comparing extubated and non-extubated groups of patients.³ Also, Unlukaplan and colleagues found that a higher mean intraoperative lactate level was a predictor of mechanical ventilation need in patients after liver transplantation.¹⁰ The same way, Skurzak et al. assigned serum lactate as one of the major criteria in the "Safe Operating Room Extubation after Liver transplantation" (SORELT) criteria, with a cut-off value of < 3.4 mmol.L⁻¹.¹¹ This lower value may be attributed to the use of cadaveric whole grafts and different surgical techniques.

Concerning blood product utilization, patients of the non-extubated group had higher transfusion rates, demonstrated by the number of intraoperatively transfused packed RBCs units. Blaszkzyc et al. mentioned that the decision regarding immediate extubation can be aided by considering the number of units of packed RBCs and fresh frozen

plasma transfused during surgery.¹² Hoffmeister and colleagues found a highly significant difference in the amount of intraoperative transfused blood products between the extubated and non-extubated groups.¹ Zeyneloglu et al., when comparing extubated with non-extubated patients, found that those extubated had lower transfusion requirements.¹³ Blood transfusion requirements were lower in our study, which may be attributed to the routine use of cell salvage, lower triggers for transfusion and different surgical techniques.

In our study, we observed a trend of longer duration of surgery among the non-extubated group, but it was not statistically significant, probably reflecting the greater difficulty in the surgical procedure. In a similar study, Bulatao and colleagues demonstrated that successful fast-tracking was significantly more likely for patients with a shorter operative time.⁹ Khosravi and colleagues when conducting their study on 200 patients undergoing liver transplantation, also found a significant difference between the extubated and non-extubated groups when comparing their operative times.¹⁴ In contradiction to our study, Hoffmeister and colleagues declared no statistically significant difference between the two groups as regards the duration of surgery.¹ Also, Biancofiore et al. found that the duration of surgery had no significant influence on the time of extubation.⁶

This study presents some major limitations, including the small sample size and the lack of investigation of additional potential predictors such as cold ischemia time, living donor age, graft size and any previous abdominal operations.

Altogether, our findings indicate that immediate extubation after liver transplantation is possible and can be safely done in a substantial percentage of cases after evaluating major factors that may affect the decision. Anesthesiologists ought to be encouraged to extend this practice to the largest possible number of patients. Successful immediate extubation may be an important indicator of the perioperative quality of care in liver transplantation.⁷ Our study demonstrated that EOS serum lactate, number of packed RBCs units transfused intra-operatively and the UOP at the neohepatic phase are good predictors of the success of immediate tracheal extubation in LDLT recipients, while MELD score has no predictive value in this matter.

Conflict of interest

The authors declare no conflicts of interest.

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