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# MELD at POD 1 as a predictor of outcome in liver allografts with peak AST >5000 U/l

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aminotransferase elevation, hepatic injury, multivariable analysis, postoperative MELD, retransplantation.

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## Summary

Perioperative liver graft injury is associated with elevation of aminotransferases after orthotopic liver transplantation (OLT). Values above 5000 U/l usually are regarded as extreme liver graft injury (ELGI). Some patients and organs recover from this critical condition. The aim of the study was to evaluate factors contributing to graft and patient survival after ELGI. From chart review we identified 64 of 917 OLT adult patients (median age 54.2 years; 68.8% males) transplanted between 11/2003 and 02/2012, who presented ELGI after OLT. Donor and recipient factors were analyzed and correlated with the outcome by univariable and multivariable methods. Multivariable cox proportional hazards showed that recipient's BMI ($P = 0.01$), model for end stage liver disease (MELD) score before OLT ($P = 0.02$) and laboratory MELD score 24 h after OLT ($P = 0.01$) were independently associated with patient survival. 30-days and 12-months survival in patients with a postoperative laboratory MELD higher than 31 was 21.4%, while patients with a postoperative laboratory MELD lower than 31 displayed 30-days and 12-months survival rates of 80% and 71.8%, respectively ($P < 0.001$). Retransplantation in the setting of ELGI after OLT should be based on all available data. Utilization of the postoperative labMELD enables the transplant physician within 24 h after transplantation to identify necessity of retransplantation objectively.

## Introduction

Liver graft injury in orthotopic liver transplantation (OLT) results in explicitly diminished survival rates of the graft and the recipient. Here, graft injury includes all damages that occur during the time of organ procurement, preservation, implantation and reperfusion. The extent of organ injury is commonly estimated by the elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) after OLT. Most studies suggest a moderate graft injury with postoperative elevation of AST and/or ALT above 1000 U/l. A severe damage of the organ is often suggested when AST and/or ALT increase above 2000 U/l and few studies indicate an elevation of AST and/or ALT above 5000 U/l as extreme liver graft injury (ELGI) [1,2]. The negative impact of a severe [3–6] or an extreme [1,2] perioperative liver graft injury on graft and patient survival has been shown in several studies. Different transplant centers suggest immediate retransplantation in case of ELGI as graft and patient survival might be considerably restricted.

Interestingly some patients and organs overcome not only a severe but even an ELGI. A retransplantation of these patients results in unnecessary danger for the patients and in wasting of scarce resources. However, it is unclear which factors promote organ and patient survival and contribute to a good clinical course, as data on this subject are rare and the existing studies describe only small patient populations [1,2].

In addition, the introduction of the MELD score based allocation systems has led to changes in organ distribution.

 

Since that time, the patient population was shifted to much sicker recipients, therefore taking influence on the overall patient survival [7,8] and probably having considerable impact on patients receiving an organ with ELGI as well. However, to our knowledge, no studies have been published dealing with this subject in the MELD era.

The aim of this study was to evaluate factors that could contribute to graft and patient survival after an ELGI of the transplanted liver.

## Patients and methods

### Study population

Data from all OLTs from November 2003 to December 2011 at the University Hospital of Essen, Germany were analyzed. This retrospective, single-center cohort study was approved by the local ethics committee and followed the Declaration of Helsinki from 1975. The ethics committee waived informed consent due to the retrospective design. While the analyses were carried out retrospectively the data was collected prospectively. All livers were recovered from deceased heart beating donors. Liver transplants into non-adult recipients (<18 years of age) were excluded from the analysis. Donor data were partly obtained from the database of the Eurotransplant International Foundation.

### Surgical procedure and immunosuppression

All organ procurements were carried out by specialized local teams according to the standards of the local procurement organizations within the different Eurotransplant regions. Decision for conducting a liver biopsy for precise microscopic assessment of steatosis or just macroscopic assessment was made by the accepting transplant surgeon of our center and upon availability. OLT was carried out with standard techniques. Venovenous bypass was not used. OLT was performed with cava replacement and end-to-end-anastomosis of portal vein, liver artery and bile duct. The perioperative intensive care and immunosuppression therapy was of similar type in all patients. The perioperative immunosuppression regimen consisted of intravenous corticosteroids (1000 mg methylprednisolone intraoperatively). Postoperative immunosuppression regimens consisted of calcineurin-inhibitors (adjusted in accordance with the trough level of the drug) in combination with corticosteroids and mycophenolate mofetil.

### Basic donor and recipient factors and technical factors for analysis

The following donor and recipient factors were analyzed for survival of ELGI after OLT: *donor*: age, gender, BMI, cause of death (cerebrovascular accident, hypoxia, trauma, others), cold ischemic time, ICU length of stay, need of vasopressor therapy (no, low, medium, high), biopsy proven steatosis (total, macrovesicular and microvesicular), rescue offer allocation, organ quality as assessed by the procurement team (good, moderate, poor), split liver transplantation, organ protection solution used during the procurement [histidin-tryptophane-ketoglutarate (HTK), University of Wisconsin (UW)], last laboratory values (AST, ALT, gGT, Bilirubin, INR, Creatinine, Serum Sodium) and the Donor Risk Index (DRI). *Recipient*: age, gender, BMI, pretransplant mechanical ventilation, pretransplant ICU stay, pretransplant hemodialysis, laboratory Model for End-stage Liver Disease (labMELD) score before transplantation, 'high-urgency' listing, time for surgical procedure, warm ischemic time, labMELD 24 h after transplantation [labMELD postoperative day 1 (POD1)], portal vein thrombosis during or within 72 h after OLT, hepatic artery thrombosis during or within 72 h after OLT, intraoperative or postoperative (within 72 h) cardiac arrest, amount of blood transfusions during OLT, transplantation before/after implementation of the MELD allocation system.

### Definition of ELGI

Postoperative injury of the transplanted liver grafts was assessed by peak aminotransferase levels in the first 72 h after OLT. Routine measurements of aminotransferases were performed every 6–8 h. Elevation of aminotransferases AST and/or ALT above 5000 U/l was defined as ELGI.

### Definition of ischemia-inducing events

Events leading to a cessation of either arterial or portal liver perfusion during OLT and in the first 72 h after OLT were defined as distinct ischemia-inducing events. Therefore, the occurrence of hepatic artery thromboses, portal vein thromboses and cardiac arrests was defined as ischemia-inducing events.

### Definition of primary non function (PNF)

PNF manifests by hepatic cytolysis, rapidly rising transaminases, absence of bile production, severe liver-related coagulation deficit, hypoglycemia, high lactate levels and hepatic hemodynamic instability [9]. In this study, PNF was defined as post-transplant liver dysfunction requiring emergency retransplantation or leading to death within 7 days. This condition was not defined based on single objective parameters, but on the repeated evaluation of all clinical data and their development over time by an interdisciplinary transplant team. Typically, these patients featured a clinical pattern with rapidly rising

aminotransferases, severe coagulopathy, dialysis dependent renal failure and high and/or increasing doses of vasopressors (e.g., norepinephrine). No certain cutoff value for any parameter was used, but the dynamics and interactions of all parameters concluded this assessment.

### Exclusion of listing for retransplantation

Patients with PNF, who required retransplantation, were accurately clinically assessed by an interdisciplinary transplant team. Dynamics and interactions of all available data were utilized to decide on existence of contraindications for retransplantation. Any condition or diagnostic finding leading to relevant elevation of risk of operation or questioning the success of retransplantation, resulting in futility, led to the decision that the patient was 'too unstable' for retransplantation. Typically, these patients presented one or several of the following conditions: progressive cardiovascular instability with vasopressor support (norepinephrine) ≥1.5 μg/kg/min and/or a cardiac index ≤3 l/min/$m^2$, sepsis, uncontrolled acidosis despite dialysis and/or infusion of alkaline equivalents, or secondary complications associated with liver dysfunction (e.g., fulminant cerebral bleeding due to coagulopathy) or the treatment modalities (e.g., intestinal ischemia). However, no ultimate cutoff values were defined, but individual decisions for each case were accomplished.

### Definition of Postoperative Model for End stage Liver Disease (labMELD POD1)

Laboratory values collected 24 h after completion of OLT were utilized to calculate the postoperative laboratory MELD score (labMELD POD1) with the same formula that is used for the commonly known laboratory MELD score. For patients receiving dialysis therapy in the postoperative course, the creatinine value was set to 4 mg/dl.

### Statistical analysis

Data were expressed as median and range values. Categorical variables were analyzed by chi-squared test. Continues variables were analyzed by the Student's *t*-test or the Mann–Whitney *U*-test. Graft and patient survival were calculated using the Kaplan–Meier method and compared with the log-rank test. Multivariable analyses were performed with the logistic regression and cox proportional hazard models. Variables with $P < 0.20$ in univariable analysis were included in an explanatory multivariable analysis, respectively [10]. Risk ratios were obtained from hazard models. Cutoff values were determined by receiver operating characteristics (ROC). Differences of $P < 0.05$ were considered to be statistically significant. Statistical analyses were performed using JMP (version 10.0.0 SAS, SAS Institute Inc., Cary, NC, USA).

## Results

Eight hundred and ninety-two patients were eligible for the assessment of elevation of aminotransferases after OLT. Finally, 64 subjects were included in the analysis, which had an elevation of transaminases AST/ALT above 5000 U/l after OLT. Median follow-up of all patients was 23.5 (0–2997) days. Median follow-up of surviving patients were 1301 (range 54–2997) days.

### Donor characteristics

Detailed donor characteristics are depicted in Table 1. Median donor age of accepted organs was 54.5 (9–77) years. 44 (68.8%) donors were men. Median donor ICU stay before donation was 4.7 days. DRI was 1.6 (0.9–2.4). Median cold and warm ischemic times of the organs were 445 (247–1090) min and 36 (16–68) min, respectively.

### Recipient characteristics

Detailed recipient characteristics are depicted in Table 1. Median age of the recipients in this study was 54.2 (20.6–74.1) years and 36 recipients (56.3%) were men. The median labMELD before OLT was 18 (range 6–40). Indications for OLT included cirrhosis related to viral hepatitis, hepatocellular carcinoma and alcoholic cirrhosis in 32.8%, 17.2% and 17.2% recipients, respectively. Median levels of aminotransferases in the first 72 h postoperatively were as follows: AST 7164 (range 5208–35607) U/l and ALT 4022 (range 833–9884) U/l.

### Ischemia-inducing events

Distinct ischemia-inducing events were observed in 10 (16.1%) cases in the present series. The exact distribution included four patients with hepatic artery thrombosis, two patients with portal vein thrombosis and four patients with cardiac arrest.

### Rate of PNF, relisting and retransplantation

PNF was described in 33 (51.6%) of 64 patients. Of these, 18 (54.5%) patients were immediately listed for retransplantation and six patients (9.4% of the overall population, 18.2% of PNF patients) received a second organ and were retransplanted within days. These six patients had different outcomes: two patients died within 30 days. All other

**Table 1.** Recipient and donor data. Data are expressed as median and range.

| | *n* = 64 |
|---|---|
| Recipient data | |
| Gender | |
| Male/Female | 36/28 (56.3%/43.8%) |
| Age (years) | 54.2 (20.6–74.1) |
| Weight (kg) | 80 (46–128) |
| Height (cm) | 170 (150–187) |
| BMI (kg/m²) | 26.1 (17.9–42.6) |
| Diabetes mellitus | 14 (23%) |
| Pre-LTX-ICU (days) | 0 (0–17) |
| Pre-LTX-mechanical Ventilation (days) | 0 (0–17) |
| Pre-LTX-Dialysis (days) | 12 (22.2%) |
| 'high-urgency' listing | 11 (18.0%) |
| TX-type | |
| Retransplantation | 3 (4.7%) |
| Combined Liver–Kidney | 3 (4.7%) |
| Right split | 4 (6.3%) |
| labMELD | 18 (6–40) |
| Warm ischemia time (min) | 36 (16–68) |
| Time for surgical procedure (min) | 337 (187–789) |
| Transfusion of erythrocytes (packs) | 5 (0–35) |
| Donor data | |
| Donor Risk Index | 1.6 (0.9–2.4) |
| Cold ischemia time (min) | 445 (247–1090) |
| Rescue offer allocation | 31 (58.5%) |
| Gender | |
| Male/Female | 44/20 (68.8%/31.3%) |
| Age (years) | 54.5 (9–77) |
| Weight (kg) | 80 (50–125) |
| Height (cm) | 176 (140–200) |
| BMI (kg/m²) | 26 (19–39) |
| Graft quality as assessed by surgeon | |
| Good | 45 (72.6%) |
| Acceptable | 17 (27.4%) |
| ICU stay (days) | 4.7 (0–30.2) |
| Vasopressor support | |
| No | 13 (24.1%) |
| Low* | 15 (27.8%) |
| Moderate* | 25 (46.3%) |
| High* | 1 (1.9%) |
| Cause of death | |
| Cerebrovascular | 37 (59.7%) |
| Trauma | 12 (19.4%) |
| Hypoxia | 4 (6.5%) |
| Other | 9 (14.5%) |
| Perfusion solution | |
| HTK | 42 (71.2%) |
| UW | 16 (27.1%) |
| Last AST (U/l) | 55 (12–725) |
| Last ALT (U/l) | 47.5 (8–639) |
| Last Bilirubin (μmol/l) | 10.1 (3.4–51.3) |
| Last γGT (U/l) | 60 (5–775) |
| Last INR | 1.11 (0.82–2.34) |
| Last Creatinine (μmol/l) | 68.7 (28.2–213.7) |
| Last Serum Sodium (mmol/l) | 148 (132–167) |
| BAR-Score | 8 (1–19) |

*Dosage of vasopressor therapy: low = <0.1 μg/kg/min, moderate = 0.1–0.5 μg/kg/min, high = >0.5 μg/kg/min).

patients are currently alive with a median survival of 2057 (range 1460–2967) days. The other 15 (45.5%) subjects of the 33 PNF patients were assessed as too unstable, indicating a contraindication for retransplantation and were not listed for retransplantation. Two patients were listed for retransplantation due to ischemia-inducing events.

Analysis of the complete cohort showed that 20 (31.3%) patients were immediately listed for retransplantation after occurrence of ELGI. A retransplantation was realized in 6 (9.4% of the overall population, 30% of listed patients) subjects. 19 (29.7%) patients with ELGI were assessed as to unstable to survive a retransplantation showing a contraindication for retransplantation. Furthermore, 25 (39.1%) patients demonstrated a clinical stable condition reflecting no indication for retransplantation and were not listed for retransplantation.

### Donor and recipient factors indicating listing for retransplantation

We retrospectively analyzed whether a delineation of recipient and/or donor factors was possible between patients listed for retransplantation and patients not listed for retransplantation after ELGI. Patients not listed for retransplantation were further divided into two groups: patients without indication for retransplantation as there clinical status was too stable and patients with contraindication for retransplantation as there clinical status was too unstable. Factors significantly different between groups are displayed in Table 2.

### Donor factors, recipient factors and graft survival

In univariable analyses lower recipient's BMI ($P = 0.04$), lower labMELD before OLT ($P = 0.02$) and lower labMELD POD1 ($P < 0.001$) were found to be significantly associated with graft survival. High-urgency listing of the recipient ($P = 0.06$) showed a tendency to be associated with graft survival in favor of patients not listed high urgently. After adjustment in the multivariable cox proportional hazard analyses, only a lower labMELD POD1 ($P < 0.001$) was significantly associated with the graft survival. Details are depicted in Table 3.

A cutoff value for the labMELD POD1 was created for the 7-day graft survival indicating immediate need for retransplantation. The ROC analysis showed that a labMELD POD1 of 31 was highly predictive for graft loss within the first 7 days after transplantation with an area under the curve of 0.904 in the same cohort. Additional analysis for the 14-day and 30-day graft survival as indicator for immediate need for retransplantation demonstrated the same results with an optimal cutoff value for the labMELDPOD1 of 31.

**Table 2.** Factors significantly different between patients not listed for ReTx (either 'too stable', or 'too unstable') and patients listed for ReTx.

| Factor | Stable, not listed $N = 25$ | Listed for ReTx $N = 20$ | Unstable, not listed $N = 19$ |
|---|---|---|---|
| Pre-OLT ICU stay (days) (Median, Q10–Q90) | 0 (0–5.6) | 0 (0–4.5) | 0.5 (0–10.5)* |
| (Mean ± SD) | 1.2 ± 4 | 0.5 ± 1.5 | 2.4 ± 4.1 |
| 'high-urgency' for first Tx (%) | 2 (8) | 1 (5.6) | 8 (42.1)* |
| labMELD before OLT | 16 (7–40) | 17.5 (7–40) | 32.5 (9–40)* |
| BAR-Score before OLT | 6 (1–19) | 5 (2–14) | 11.5 (3–18)* |
| Rescue Offer Organ (%) | 15 (71.4) | 10 (66.7) | 5 (26.3)* |
| Postoperative dialysis (%) | 11 (45.8)† | 17 (85) | 19 (100) |
| PNF (%) | 0 (0)† | 18 (90) | 15 (78.9) |
| labMELD POD1 | 22.4 (8.1–40.6)† | 35.7 (10.7–42.4) | 32.6 (23.9–40) |

*$P < 0.05$ versus 'stable' and 'listed for ReTx'.
†$P < 0.05$ versus 'unstable' and 'listed for ReTx'.

### Donor factors, recipient factors and patient survival

To identify factors that promote survival of patients with an allograft with ELGI all patients retransplanted in the further course were excluded from this analysis. In the univariable analyses, a lower recipient's BMI ($P = 0.02$), recipient nonhigh-urgency listing ($P = 0.04$), a lower labMELD before OLT ($P = 0.01$) and a lower labMELD POD1 ($P < 0.001$) were found to be significantly associated with patient survival. After adjusting for confounders by multivariable cox proportional hazard analysis, the lower recipient's BMI ($P = 0.01$), lower labMELD before OLT ($P = 0.02$) and lower labMELD POD1 ($P = 0.01$) were independently associated with patient survival. Details are depicted in Table 3.

**Table 3.** Multivariable cox proportional hazards for graft and patient loss.

| | Risk ratio | 95% CI | *P*-value |
|---|---|---|---|
| Patient loss | | | |
| Donor vasopressor support | 2.72 | 0.03–26.8 | 0.96 |
| Rescue offer | 4.01 | 0.81–25.64 | 0.09 |
| Recipient gender | 3.51 | 0.79–23.97 | 0.10 |
| Recipient BMI | **1.12** | **1.03–1.22** | **0.01** |
| labMELD before transplantation | **1.1** | **1.01–1.19** | **0.02** |
| High-urgency listing | 1.51 | 0.24–8.99 | 0.65 |
| Time for surgery | 1.00 | 0.99–1.01 | 0.38 |
| labMELD pOP1 >31 | **4.68** | **1.55–15.94** | **0.01** |
| Graft loss | | | |
| Rescue offer | 4.30 | 0.81–26.88 | 0.09 |
| Recipient gender | 2.58 | 0.78–10.51 | 0.12 |
| Recipient BMI | 1.07 | 0.99–1.15 | 0.07 |
| labMELD before transplantation | 1.06 | 0.98–1.14 | 0.14 |
| High-urgency listing | 1.84 | 0.38–9.85 | 0.45 |
| R-DM | 1.13 | 0.34–3.48 | 0.83 |
| Time for surgery | 0.99 | 0.99–1.00 | 0.57 |
| labMELD pOP1 >31 | **12.04** | **3.94–40.77** | **<0.001** |

Bold letters indiciating significant values.

### Patient and graft outcome

Overall, 64 patients were included into the study. After 30 days, the graft survival rate was 40.6%. The 12 months overall graft survival rate was 35.8%. The 30 days patient survival rate was 46.8%, and the 12 months patient survival rate was 42.8%, accordingly.

As the labMELD POD1 demonstrated the statistically highest significance for patient and graft survival in the multivariable cox proportional hazard analysis, survival rates in dependence of the labMELD POD1 were illustrated. Here, the 30 days graft survival rate for patients with a labMELD POD1 score higher than 31 was 7.2%. Patients with a labMELD POD1 lower than 31 demonstrated a 30 day graft survival of 80%. After 12 months, patients with a labMELD POD1 higher than 31 showed a graft survival rate of 7.2% compared with a graft survival rate of 71.8% in patients with a labMELD POD1 lower than 31 ($P < 0.001$). The overall patient survival after 30 days and 12 months in patients with a labMELD POD1 higher than 31 was 21.4%, respectively. Patients with a labMELD POD1 lower than 31 displayed survival rates of 80% and 71.8% after 30 days and 12 months, respectively ($P < 0.001$) (Fig. 1).

As retrospectively assessed, three groups of patients experiencing ELGI could be delineated in terms of listing for retransplantation. Patients listed for retransplantation (and subsequently retransplanted if an organ became available) showed survival rates of 30% after 30 days, 12 months and 5 years, respectively. Patients not listed for retransplantation displaying no indication for retransplantation as they were assessed as too stable showed a 30 day survival of 88%, a 12 months survival 83.8% and a 5 year survival of 56%. Patients not listed for retransplantation demonstrating a contraindication for retransplantation as they were assessed as too unstable showed survival rates of 5% and

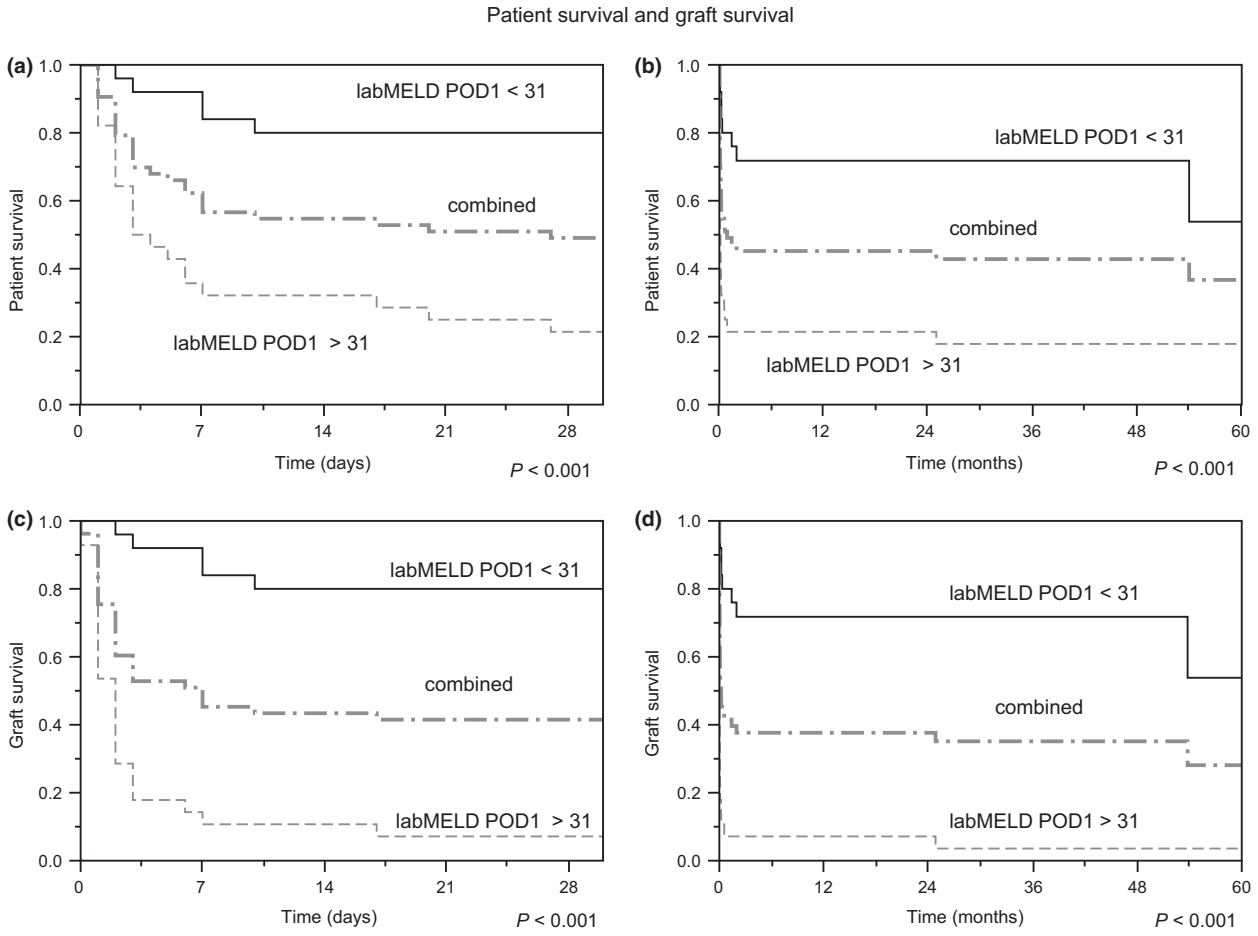


**Figure 1** Patient and graft survival according to a postoperative labMELD lower and higher than 31. (a) 30 days patient survival. (b) 5 year patient survival. (c) 30 days graft survival. (d) 5 year graft survival.

0% after 30 days and 12 months, respectively ($P < 0.001$) (Fig. 2).

The median hospital stay of all patients was 18 (0–169) days with a median ICU stay of 6 (0–161) days. As several patients died early within the hospital stay, we analyzed the survivors separately: median hospital stay of all surviving patients was 33 (16–100) days with a median ICU stay of 7 (2–57) days.

42.2% of patients ($n = 27$) with an ELGI were discharged from the hospital alive. These patients showed a close to ideal survival rate of 100% after 30 days and 12 months and of 72.2% after 5 years.

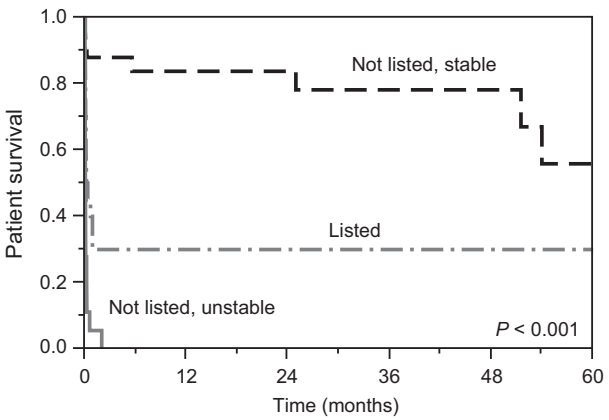


**Figure 2** Patient survival according to postoperative scheme of listing for retransplantation.

### Ischemia-inducing events and outcome

Patients with HAT were handled by surgical reintervention in all four cases. Arterial thrombectomy was successful in these cases. Afterward a sufficient arterial flow was observed at all times during follow up. One patient was relisted with 'high-urgency' status, but no organ was allocated to this patient. This patient died on POD 2 for poor organ function. The other three patients did not require retransplantation and are currently alive for 50.4, 45.1 and 40 months after OLT.


 

Occurrence of portal vein thrombosis was handled by surgical reoperation in both cases in the present series with successful thrombectomy by fogarty catheters. Nonetheless, both patients died on POD 1 and POD 2 due to poor graft function. One patient was listed for retransplantation with high-urgency status. No graft became available before the patient died. The other patient was assessed as to ill to survive a retransplantation. Accordingly, he was not listed for retransplantation and died. Only one patient who experienced cardiac arrest during or shortly after OLT was discharged from hospital alive. The other three patients died in hospital with different causes of death, without direct association with liver injury: The first one died because of pulmonary embolism at the first day after transplantation. The second one died because of bilateral cerebral infarction on POD 6. The third patient passed away on POD 27 because of fungal sepsis.

## Discussion

Aim of this study was to evaluate recipient factors that contribute to the survival of graft and patient after an ELGI of the transplanted liver. The presented results showed that three fundamental factors impact the patient survival: a higher BMI of the recipient, higher labMELD score before transplantation and higher labMELD POD1 were independently associated with patient loss. In terms of graft survival, only the labMELD POD1 was independently associated with the outcome. At this point, it becomes clear that the identification of patients and allografts surviving this dangerous complication seems possible already within the first 24 h after transplantation. So, vice versa irreversible functional impairment might be recognized within 24 h after liver transplantation. Indeed, it is of major interest that an early diagnosis is possible for this critically ill patients, where holding of on decision-making is not an option. Figure 1 illustrates the dramatic role of the labMELD POD1. Patients with a labMELD POD1 lower than 31 points have an approximately three- to fivefold augmented probability to survive an ELGI during OLT.

In fact, decision for retransplantation should be based on three major aspects: First of all, the probability of spontaneous organ recovery should be low, so that unnecessary hazards for the patients are spared. Second, prospects of success have to be considered. Patients too ill to survive the procedure of retransplantation would not benefit by futile efforts, which then represent organ wastage. Third, survival rates after retransplantation have to be kept in mind. Recent data demonstrated significantly inferior survival rates for retransplantations in the first 7 days [11] with 1-year survival of approximately 65%.

With these aspects in mind, the chosen cutoff value for the labMELD POD1 of 31 attracts special interest. Beside its high impact on the graft survival and its high predictive value, this discriminator led to a patient survival of more than 70% after 1 year, thus being at least similar to survival rates after early retransplantation. So, retransplantation of patients with an ELGI and a labMELD POD1 lower than 31, would not improve the prognosis for these patients and cannot be recommended based on the present data. Additionally, such retransplantations would be a waste of a scarce resource. Reduction of the labMELD POD1 threshold might increase the survival rate, but on the other hand will lead to unnecessary retransplantations. Future prospective studies should validate this threshold.

Different entities (e.g., ischemic necrosis, transient circulatory disturbances, ischemia-inducing events, etc.) result in a similar biochemical postoperative pattern of ELGI. The postoperative labMELD score seems to be able to discriminate transient from persisting impairments of the grafts, comprehensively. It should be kept in mind that perioperative coagulation management and preoperatively elevated levels of bilirubin, which fall slowly after OLT, impact calculation of the postoperative labMELD score. Other classifications use values at a later point of time, accordingly [4]. Nonetheless, the role of the postoperative labMELD has been recognized by other studies recently too [12]. An immediate sufficient assessment is essential after occurrence of an ELGI after OLT. Waiting for several days is not an option in this special scenario, so that the labMELD POD1 with all its restrictions might help in the clinical decision-making.

Retrospective analysis of the current cohort showed significant differences between patients that were listed for retransplantation and patients that were assessed as too unstable (contraindication) or too stable (no indication) for retransplantation (Table 2). The data suggests that recipient's clinical status and severity of disease before transplantation affected the decision to identify a patient as too unstable for listing, in contrast to postoperative outcome parameters. These were used to identify patients that had a better prognosis and were too stable. More advanced disease severity before transplantation usually adds up to worse clinical situations with less capacity of the patient to overcome a critical condition like an ELGI, explaining the relevance of the pretransplant factors.

While patients assessed as too unstable might not benefit from the results of this study, the other two groups should be focused on: these are patients in high risk situations, where objective assessment criteria are lacking. Providing objective parameter (like labMELD POD1) might help the clinician to accelerate the decision-making process what is of utmost importance for these patients.

Survival rates of these patient populations indicate that the decisions made were reasonable (Fig. 2): all patients too unstable for retransplantation died promptly. Patients

relisted for OLT survived only if another organ for retransplantation became available in a reasonable time period, stressing that this was their only chance to survive the critical condition. Moreover, patients without indication for retransplantation showed normal survival rates for the first year after OLT in the EUROTRANSPLANT area [7,13,14] while the 5 year survival rate was diminished (Fig. 2). Further research might analyze long-term follow-up and outcomes in detail.

Interestingly, slightly less than half of all patients experiencing ELGI after OLT are discharged alive from hospital, then demonstrating excellent follow-up courses with 1 year survival of 100% and 5 year survival rates as high as the overall liver transplantation population [15].

Ischemia-inducing events were not identified as a specific risk factor in this analysis. Certainly, the numbers of ischemia-inducing events in the present cohort were too small for a well-grounded statistical approach. As ischemia-inducing events contribute to the heterogeneity of the cohort, we performed the presented analyses additionally after exclusion of those patients (data not shown). This did neither impact the results of the analysis nor the conclusion of the study. The clinical courses of these patients indicate that a retransplantation should be discussed thoroughly, especially after PVT or cardiac arrest.

Interestingly, outstanding and well accepted classification systems like the DRI [16] and the BAR-score [17] were not able to discriminate between patients with a good or a poor clinical course after ELGI. This might be due to the fact that these are designed to predict the outcome of overall populations and not highly specialized populations like the presented cohort.

Up to our knowledge, this is the first report on risk factors for graft and patient survival in patients with an ELGI after OLT in the MELD era. Indeed, era of transplantation (pre versus post MELD implementation) did not impact the outcome, presumably due to the critical ill population under investigation, with other factors being pivotal.

Some limitations of the present study should be kept in mind for a reasonable interpretation of the data: first, the group size is rather small, limiting all statistical approaches and their validity. In addition, this cohort of patients and the entities leading to ELGI are heterogeneous. Furthermore, in the special scenario of ELGI, the criteria for PNF and clinical prerequisites entailing retransplantation in each transplant center might bias the resulting data. Therefore, transferring these data on other populations with PNF or ELGI should be approached with caution and the definitions given in the study should be kept in mind. However, we are convinced that the factors described in the present study represent a current standard of treatment.

## Conclusion

We want to stress that we do not promote to wait for an organ to fail without taking action, but aim at reducing unnecessary retransplantations for patients with a borderline indication. The present study revealed the recipient's labMELD before OLT, the recipient's BMI and the labMELD POD1 as factors associated with patient survival. Indeed, utilization of the labMELD POD1 enables the transplant physician within 24 h after transplantation to assess allograft function objectively, and indicate the necessity of retransplantation in the setting of ELGI. Future prospective studies should validate this finding.

## Authorship

DPH: study design, data collection, statistical analysis, data interpretation, manuscript preparation and literature search. GCS: statistical analysis, data interpretation and manuscript preparation. FHS and JWT: data collection, data interpretation and manuscript preparation. AP: study design, data interpretation, manuscript preparation and literature search. ZM: study design, data collection, data interpretation, manuscript preparation and literature search.

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