TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Liver transplantation for acute liver failure: are there thresholds not to be crossed?

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Keywords
medical decision making, multivariable analysis, pH, preoperative assessment, risk factors.

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Conflict of interest
The authors have no conflict of interest to declare as described by *Transplant International*.

Received: 10 November 2013
Revision requested: 12 December 2013
Accepted: 3 March 2014
Published online: 23 April 2014

doi:10.1111/tri.12302

Summary

Factors predicting survival after liver transplantation (LT) for irreversible acute liver failure (ALF) are rare. The aim of this study was to identify prognostic preoperative factors of patients with ALF that predict mortality after LT to avoid futile transplantation. From chart review, we identified 57 patients receiving transplants for ALF from 12/2000 to 09/2010. Recipient and donor data were analyzed and correlated with in-hospital mortality and patient survival by univariable/multivariable logistic regression and Cox proportional hazards. The survival rates at 30 days and 12 months were 77.2% and 64.9%, respectively. The in-hospital mortality rate was 29.8%. Follow-up of patients discharged from the hospital alive showed 30-day and 12-month survivals of 100% and 92.5%, respectively. Multivariable analysis of factors known preoperatively showed that the lowest pH of the recipient before LT ($P = 0.03$) was independently associated with in-hospital mortality, and the recipient's BMI ($P = 0.03$) and the lowest pH before LT ($P = 0.03$) were independently associated with patient survival. A pH of 7.26 was the calculated cutoff (ROC) for increased in-hospital mortality. Donor factors did not affect patient survival. Patients with ALF and a pH $\leq$ 7.26 have the worst outcome after liver transplantation. Therefore, emergency liver transplantation should be critically discussed for each individual.

Introduction

Acute liver failure (ALF) is a rare but devastating clinical syndrome and is characterized by the sudden onset of hyperbilirubinemia, hepatic encephalopathy and coagulopathy with no pre-existing liver disease [1,2]. Currently, ALF remains a life-threatening condition. Spontaneous survival rates depend on the underlying disease and location and are reported to range from 17% to 68% [3]. As emergency liver transplantation (LT) became available, survival rates have been reported between 60% [4] and 79% [5–7].

Most studies analyzing cohorts of patients with ALF have focused on the factors that determine the need for LT as a rescue therapy [8–12], while studies defining the risk factors for a poor outcome of transplant candidates for ALF are rare. The existing studies are either too small or analyze highly specific subgroups [13]. In particular, analyses of registry data, which included large numbers of patients, are of special interest [5,14]. Unfortunately, those are limited due to the shallow parameters available for evaluation in the registry databases. Indeed, in addition to urgency in terms of disease severity, the prospect of success is designated as one of the major goals of liver transplantation.

The acceptance of a high-urgency listing for ALF at the Eurotransplant foundation is partly based upon the Kings College (KC) criteria [15]. However, the KC criteria provide a positive predictive value of 85% and a negative predictive value of 50%, which means that 15% of transplants

depending on these criteria are futile and burden the donor pool. Another group of patients with liver failure consists of those who need a transplant but are in such poor condition that they would not survive even with a successful transplantation. These transplants are futile, as well.

Therefore, the aim of this study was to identify prognostic preoperative factors of patients with ALF predicting mortality after LT to avoid futile transplantations.

Patients and methods

Study population

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. The data from all LTs from December 2000 to September 2010 at the University Hospital of Essen, Germany, were analyzed. All of the livers were recovered from deceased heart-beating donors. Liver transplants into nonadult recipients (<18 years of age) were excluded from the analysis. The donor data were partly obtained from the database of the Eurotransplant International Foundation.

Surgical procedure and immunosuppression

All of the transplantations were performed using standard surgical techniques, and a standardized anesthesia protocol was applied to all of the patients. Patients were treated postoperatively in a single intensive care unit applying standardized care consisting of triple immune suppression (corticosteroids, mycophenolate mofetil and tacrolimus or cyclosporine A).

Criteria for liver transplantation in the setting of acute liver failure

Indication for liver transplantation in the setting of ALF is bound to the German transplant law and the guidelines of the Eurotransplant foundation. For the present series, the Kings college criteria were utilized for the majority of patients. Patients with hepatitis B-induced ALF were listed in accordance to the Clichy criteria.

Donor and recipient factors for analysis

The following donor and recipient factors were analyzed for in-hospital mortality and overall survival of patients receiving LT for acute liver failure:

Donor

Gender, height, weight, BMI, cold ischemic time, need of vasopressor therapy [no, low (<0.1 μg/kg/min), moderate (0.1–0.5 μg/kg/min), high (>0.5 μg/kg/min)], incidence of hypotensive periods, incidence of cardiac arrest, organ quality as assessed by the procurement team (good, moderate, poor), perfusion quality as assessed by the procurement team (good, moderate, poor), serology (HBsAG, HBcAB, HCV AB, HIV AB, CMV IgG, Lues AB,), graft type (split, whole) and the donor risk index.

Recipient

Age, gender, height, weight, BMI, reason for acute liver failure, health insurance status, parameters of ICU treatment before LT (mechanical ventilation, highest PEEP, Horowitz index, highest central venous pressure, need of and dosing of vasopressor), administration of blood products before LT (total prothrombin complex concentrate (4 factor concentrate), total fibrinogen, total fresh-frozen plasma, prothrombin complex concentrate and fibrinogen in the last 24 h), intraoperative administration of blood products (prothrombin complex concentrate, fibrinogen, fresh-frozen plasma and erythrocytes packs), laboratory values of admission (AST, ALT, total bilirubin, INR, Quick, fibrinogen, lactate, creatinine), pre-LT hemodialysis, lactate 24 h before LT, lowest pH before LT, maximum of base excess before LT, laboratory MELD score before LT, development of early allograft dysfunction (EAD) after LT, incidence of bacterial and fungal sepsis after LT, laboratory values on postoperative day 1, day 3 and day 7 (AST, ALT, total bilirubin, INR, Quick, fibrinogen, creatinine), need for hemodialysis in the postoperative course, the calculated laboratory MELD score on postoperative day 1, day 3 and day 7 and blood group compatible transplantation.

Definition of early allograft dysfunction

Early allograft dysfunction (EAD) was defined as: bilirubin ≥10 mg/dl on postoperative day 7 and/or INR ≥ 1.6 on postoperative day 7 and/or AST or ALT > 2000 U/l within the first 7 days [16]. Each case was classified as "EAD" or "no-EAD". For recipients who died within 7 days after transplantation, laboratory and clinical parameters up to the time of death were considered for the classification.

Definition of postoperative model for end-stage liver disease (labMELD POD)

Laboratory values collected 24, 72 and 168 h after completion of LT were utilized to calculate the postoperative labMELD score (labMELD POD1, POD3 and POD7) with the same formula that is used for the commonly known laboratory MELD score. For patients who had dialysis in the postoperative course, the creatinine value was set to 4 mg/dl.

Statistical analysis

The data were expressed as mean and standard deviation and median and range values as appropriate. Graft and patient survival were calculated using the Kaplan–Meier method and were compared using the log-rank test. Univariable and multivariable analyses were performed with logistic regression and Cox proportional hazard models. Variables with $P < 0.05$ in univariable analysis were included in the multivariable analysis. Risk ratios or odds ratios were obtained from hazard models. Cut-off values were determined with ROC analysis. The level of missingness for all variables was lower than 5% unless otherwise indicated. Missingness was handled by case exclusion. 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

A cohort of 1144 patients received transplants between December 2000 and September 2010 at the University Hospital Essen. Ultimately, 57 (5%) subjects transplanted for acute liver failure were identified from the chart review. All transplantations were carried out for acute liver failure, meaning onset of jaundice to development of hepatic encephalopathy between 8 and 28 days, according to the criteria by O'Grady and colleagues [17]. The median follow-up of all the patients was 57.4 (0–150) months. The median follow-up of the surviving patients was 69.7 (range 26.4–150) months.

Donor characteristics

The mean donor risk index of accepted organs was 1.6 (0.95–2.4), and 21 (39.6%) donors were men. The median BMI of donors was 23.9 (18.3–35.2) kg/m². A total of 13 (24.5%) donors experienced a hypotensive period, and 13 donors experienced a cardiac arrest before the procurement surgery. The dosing of vasopressors was documented as follows: 1 (2.3%) donor with none, 16 (36.4%) donors with low, 16 (36.4%) donors with moderate and 11 (24.9%) donors with high vasopressor support. Organ quality was described as "good" in 45 (91.8%) and as "acceptable" in 4 (8.2%) cases by the procurement teams. Organ perfusion was described as "good" in all cases by the procurement teams. No donors were positive for HBsAG, HBcAb, HCVAb, LuesAb or HIVAb. In total, 27 (57.4%) donors were positive for CMV IgG. The mean cold ischemic times of the organs were 383.5 (162–840) min. Neither split grafts nor AB0 incompatible grafts were utilized in the presented series.

Recipient characteristics

The median age of the recipients in the present study was 36 (17–67) years, and 20 recipients (35.7%) were men. The mean BMI of all the recipients was 25.3 (17.9–36.7) kg/m². The median labMELD before LT was 30.6 (range 16.6–48.4). All patients presented with hepatic encephalopathy grade II–III. Thirty-seven (66.1%) patients needed mechanical ventilation before LT and showed an accompanying median highest PEEP of 5 (5–15) mmHg. The median Horowitz index before LT was 285 (63.6–540), and 18 (32.7%) recipients were in need of hemodialysis before LT. The median central venous pressure was 13 (4–25) mmHg. Details of the administration of blood products before and during LT are depicted in Table 1. Reasons for acute liver failure included viral hepatitis, drug intake (which included four patients with acetaminophen intoxication), idiopathies, Wilson's disease and others in 22.8%, 22.8%, 22.8, 14.0% and 17.5% of recipients, respectively. The median levels of preoperative and postoperative laboratory values at day 1, 3 and 7, including the calculated postoperative labMELD score, are shown in Table 2.

Donor and recipient factors and in-hospital mortality

We analyzed whether a delineation of preoperatively known recipient and/or donor factors was possible between patients who died in the hospital and patients who were discharged from the hospital alive. Univariable analysis (Table 3) showed that the patients who were discharged from the hospital alive had significantly lower recipient BMIs [24.1 (18.3–34.6) kg/m²], lower peak central venous pressures before LT [11 (4–21) mmHg] and higher lowest pH before LT [7.39 (7.21–7.5)] when compared to patients who died in-hospital (BMI 28.5 (17.9–36.7) kg/m² ($P = 0.01$), highest central venous pressure before LT 15 (5–25) mmHg ($P = 0.02$), lowest pH before LT 7.3 (7.11–7.46) ($P = 0.01$)). The recipient age, mechanical ventilation before LT and conduction of hemodialysis before LT

Table 1. Application of blood products before and during liver transplantation (LT).

Parameter	Pre-LT total	Pre-LT 24 h before	During LT
PCC (units)*	2000 (0–18 000)	2000 (0–9000)	0 (0–6000)
Fibrinogen (g)	2 (0–23)	0 (0–16)	2 (0–14)
Fresh-frozen plasma (packs)	0 (0–72)	–	7 (0–32)
Erythrocytes (packs)	–	–	6 (0–20)

Data expressed as median and range.
*PCC, prothrombin complex concentrate (4-factor concentrate).

Table 2. Distribution of laboratory values before and after liver transplantation (LT).

Laboratory parameter	Admission	pOP1	pOP3	pOP7
AST (U/l)	569 (44–18 139)	676 (60–13 574)	155 (20–5489)	64.5 (13–2917)
ALT (U/l)	992 (10–8976)	771 (94–7130)	515 (61–3618)	158.5 (57–1322)
Bilirubin (mg/dl)	18 (2.7–48.6)	5.9 (0.8–29.9)	4.25 (0.5–23.1)	3.5 (0.8–21.7)
INR	2.61 (1.54–8.17)	1.43 (0.97–3.24)	1.17 (0.86–2.3)	1.03 (0.89–3.28)
Quick	27 (5–49)	56 (18–120)	87 (30–120)	99 (19–120)
Fibrinogen (mg/dl)	154 (50–1000)	224 (70–449)	325 (118–710)	460 (70–1000)
Lactate (mM)	2 (0.6–27)	–	–	–
Creatinine (mg/dl)	1.05 (0.47–8.2)	3.6 (0.6–4.9)	2.1 (0.5–4.4)	1.32 (0.33–5.03)
labMELD pOP	–	24.9 (8–39.7)	19.4 (6.4–37.3)	13.5 (6.4–40)

Data expressed as median and range. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

demonstrated tendencies to predict in-hospital mortality. In multivariable analysis, only the lowest pH before LT was found to be an independent predictor of in-hospital mortality ($P = 0.03$) (Table 4).

Including factors into the multivariable approach that were not known until the postoperative course showed that the recipient BMI ($P = 0.04$), lowest pH before LT ($P = 0.01$) and the value of AST at POD1 ($P = 0.01$) were independently associated with in-hospital mortality. The occurrence of poor graft function as determined by the incidence of EAD showed only a tendency to be associated with a poorer outcome in univariable analysis ($P = 0.07$).

A cutoff value for the lowest pH before LT was created for in-hospital mortality, indicating a high risk for liver transplantation in the setting of ALF. The ROC analysis showed that a lowest pH of lower than 7.26 was highly predictive for in-hospital mortality with an AUC of 0.75.

Donor factors, recipient factors and patient survival

In univariable Cox proportional hazard analyses of factors known preoperatively, the recipient BMI ($P = 0.03$), the labMELD before LT ($P = 0.049$) and the lowest pH before LT ($P = 0.01$) were found to be significantly associated with patient survival. After adjustment in the multivariable Cox proportional hazard analyses, only the recipient BMI ($P = 0.03$) and the lowest pH before LT ($P = 0.03$) were significantly associated with patient survival. Details are shown in Table 5. Further adjustment of donor and recipient factors that were not known until the postoperative course showed that only the values of AST at POD1 ($P = 0.02$) and the labMELD POD1 ($P = 0.01$) were independently associated with recipient survival.

Patient outcome

Overall, 57 patients were included in the study. The overall 30-day patient survival rate was 77.2%, and the 12-months patient survival rate was 64.9%.

As the lowest pH before LT demonstrated the highest significance for in-hospital mortality and patient survival, a threshold was calculated by ROC analysis. The resulting cutoff value for a poorer prognosis was 7.26. Accordingly, the survival rates for recipients with a pH lower and higher than 7.26 were calculated. Here, the 30-day graft, 12-month and 60-month survivals for patients with a lowest preoperative pH lower than 7.26 were 28.6%, 14.3% and 14.3%, respectively. Patients with a lowest preoperative pH higher than 7.26 showed a 30-day survival rate of 82.2%, a 12-month survival rate of 68.9% and a 60-month survival rate of 68.9% ($P < 0.001$) (Fig. 1).

The in-hospital mortality rate was 29.8% (17 subjects), while 70.2% (40 subjects) were discharged from the hospital alive. A follow-up of patients discharged from the hospital showed a 30-day, 12-month and 60-month survival of 100%, 92.5% and 92.5%, respectively (Fig. 2).

Early allograft dysfunction (EAD) occurred in 20 (35.1%) of 57 patients. Interestingly, this condition, which is reflective of early poor graft function after LT, did not have any relevance for patient survival, with similar survival rates in EAD and non-EAD patients ($P = 0.36$).

In terms of infectious complications after LT, 14 (24.6%) patients developed bacterial sepsis during the follow-up. In addition, 2 (11.8%) subjects showed fungal infections during the post-transplant course.

Persisting neurological deficits were not observed in any patient after LT.

The causes of death after LT for ALF [21 subjects (36.8%)] were as follows: four cardiovascular (19.0%), two cerebrovascular (9.5%), eight infectious (38.1%), one malignancy occurrence (4.8%), one allograft failure (4.8%) and five others causes (23.8%). In the two different groups, the following distribution of causes of death was documented: in patients with a lowest pH higher than 7.26 cardiovascular events in 26.7%, cerebrovascular events in 6.7%, primary nonfunction in 6.7%, infectious complications in 13.3% and other causes in 26.7%. Infectious complications occurring more than 1 year after transplantation

Table 3. Univariable analysis of donor and recipient details for in-hospital mortality.

	In-hospital death n = 17 (29.8%)	Living discharge n = 40 (70.2%)	P-value
Donor data			
Gender			
Male (%)	7 (41.2)	14 (37.8)	0.69
Female (%)	10 (58.8)	23 (62.1)	
BMI (kg/m²)	23.9 (18.3–28.4)	23.9 (18.3–35.2)	0.55
Organ quality as assessed by surgeon			
Good (%)	13 (86.7)	32 (94.1)	0.4
Moderate (%)	2 (13.3)	2 (5.9)	
Poor (%)	0 (0)	0 (0)	
Cardiac arrest (%)	5 (31.3)	8 (21.1)	0.43
Vasopressor support			
No (%)	5 (38.5)	1 (3.2)	
Low (%)	4 (30.8)	23 (74.1)	0.83
Moderate (%)	1 (7.7)	3 (9.7)	
High (%)	3 (2.3)	4 (12.9)	
CMV IgG positive (%)	11 (73.3)	16 (40)	0.13
Cold ischemic time (min)	361 (162–840)	383.5 (235–786)	0.63
Donor risk index	1.7 (1.1–2.2)	1.5 (0.95–2.4)	0.53
Recipient data			
Gender			
Male (%)	8 (47.1)	12 (30.8)	0.25
Female (%)	9 (52.9)	27 (69.2)	
Age (years)	43 (19–65)	35.5 (17–67)	*0.06*
labMELD before LT (%)	32.7 (17.3–48.4)	28.9 (16.4–43.9)	0.25
Private health insurance (%)	4 (25)	8 (34.8)	0.51
BMI (kg/m²)	28.5 (17.9–36.7)	24.1 (18.3–34.6)	0.01
Pre-LT mechanical ventilation (%)	10 (58.8)	27 (69.2)	*0.09*
Highest PEEP pre-LT (mmHg)	7.5 (5–15)	5 (5–10)	0.39
Horowitz index pre-LT (mmHg)	280.5 (127.3–540)	316.7 (63.6–493.3)	0.71
Highest central venous pressure pre-LT (mmHg)	15 (5–25)	11 (4–21)	**0.02**
Vasopressor support			
No (%)	3 (18.8)	18 (62.1)	
Low (%)	6 (37.6)	2 (6.9)	
Moderate (%)	2 (13)	6 (20.7)	0.32
High (%)	3 (18.8)	3 (10.3)	
Lowest pH pre-LT	7.3 (7.11–7.46)	7.39 (7.21–7.5)	**0.01**
Lactate 24 h pre-LT (mM)	3 (1.4–30)	3 (0.8–14.1)	0.40
Hemodialysis pre-LT (%)	9 (52.9)	11 (27.5)	*0.07*
EAD (%)	9 (52.9)	11 (27.5)	*0.07*

Data are expressed as median and range (Vasopressor dosage: low < 0.5 μg/kg/min, moderate = 0.5–1.0 μg/kg/min, high > 1.0 μg/kg/min). labMELD, laboratory model for end-stage liver disease; LT, liver transplantation; EAD, early allograft dysfunction.
P-values < 0.05 in bold. *P*-values < 0.1 in italics.

Table 4. Multivariable logistic regression of preoperative recipient and donor details and in-hospital mortality.

	Odds ratio	P-value
Recipient BMI	0.91*	0.27
Highest CVP before LT	0.89*	0.16
Lowest pH before LT	248.85†	**0.03**

*Odds referring to change of 1 unit in the regressor.
†Odds referring to change of 1/10 unit in the regressor.
P-values < 0.05 in bold.

Table 5. Multivariable Cox proportional hazard analysis of preoperative donor and recipient details and patient survival.

	Risk ratio	P-value
labMELD before LT	1.02*	0.44
Recipient BMI	1.11*	**0.03**
Lowest pH before LT	30.14†	**0.03**

*Risks referring to change of 1 unit in the regressor.
†Risks referring to change of 1/10 unit in the regressor.
P-values < 0.05 in bold.

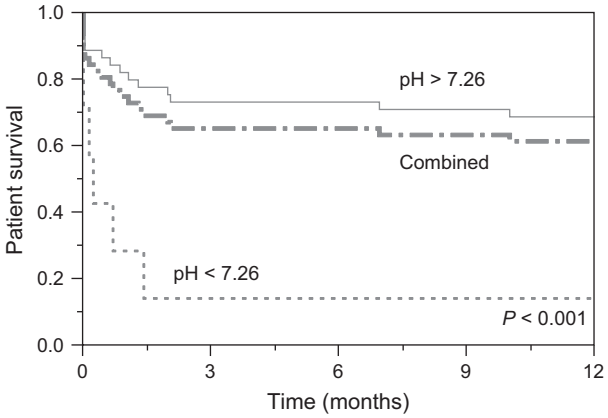

Figure 1 Patient survival according to lowest preoperative pH.

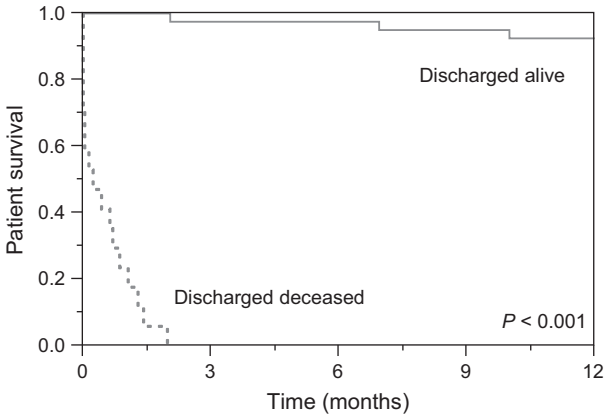

Figure 2 Patient survival according to postoperative discharge from hospital.

accounted for 13.3% of deaths in this group. Additionally, in 6.7% malignancy was documented as cause of death.

In patients with a lowest pH lower than 7.26 causes of death included cerebrovascular events in 16.7%, infectious causes in 66.7% and other reasons in 16.7%.

Discussion

The aim of this study was to evaluate prognostic preoperative factors of donors and recipients to predict mortality of patients undergoing LT for acute liver failure to avoid futile transplantations.

Definition of futility in the setting of ALF is of major interest. Unfortunately, no consistent definition exists, and recently published works demonstrated that ongoing elaborate discussion of medical, ethical and social aspects have to be taken into account [18]. One accepted definition describes futility as 3-month or in-hospital mortality [19].

The presented results show that two fundamental preoperative factors significantly impacted patient survival: the recipient BMI and the lowest pH before LT. More precisely, higher recipient BMI values and lower recipient pH values increased the risk of mortality following LT. For in-hospital mortality, only the pH of the recipient before LT remained an independent predictor in multivariable analysis. The risk ratio of the factors indicated that the lowest pH before LT had the highest impact on the overall patient survival (Table 3). Patients with a preoperative pH higher than 7.26 had an approximately three- to fivefold increased probability of surviving LT in the setting of ALF. In fact, only a seventh of all subjects presenting a pH lower than 7.26 before LT survived longer than 1 year (Fig. 1). The causes and timing of death in patients with a preoperative pH higher than 7.26 compared to the patients with a preoperative pH lower than 7.26 indicate that different risk profiles exist between groups. Although a rational statistical analysis between groups was not possible (due to the small numbers of events), the logical comparison demonstrates the increased risk of infectious complications and death for patients with a pH lower than 7.26, what could be due to an overall reduced clinical condition and accordingly reduced immunocompetence. In fact, the short-term mortality is a key issue after transplantation for ALF. Therefore, even more and intensified attention should be drawn to possible infectious foci in patients with a preoperative pH lower than 7.26. Precise diagnostic in combination with early and meticulous treatment, maybe even preventive treatment, might be a way to reduce the mortality in this group.

The utilization of preoperative pH values must be specifically addressed, as the pH of the patients in this patient population had been iatrogenically influenced. The application of buffering substances, such as sodium bicarbonate or Tris, is routinely performed for compensation reasons. Nonetheless, patients with a low pH can be assumed to have had lower values than patients with a close to normal or normal pH, as complete compensation is usually not aimed for. Thus, the pH may be used as a clinical indicator despite some limitations.

It is quite interesting that the pH serves as an indicator for the need of transplantation in ALF and as an indicator of restricted outcome after transplantation. It should be underscored that only a minority of patients (7%) were transplanted for ALF in the setting of acetaminophen intoxication. As these patients display an indication for LT by a decrease of pH < 7.3, the use of pH as a limiting factor for transplantation should not be valued for acetaminophen intoxication [20]. Nonetheless, this interaction of the pH as an indicator for poor outcome without LT and a risk factor for poor outcome after LT is not contradictory, but underscores the serious conditions of patients with a low

pH before transplantation. It is of paramount importance to include other risk factors and all available data in such setting and assess each patient individually.

To strengthen the analysis evidence, we introduced factors into the multivariable model that were unknown preoperatively but became evident in the postoperative course and were significantly tested in the univariable analysis. The lowest pH before LT, the recipient BMI and the peak AST at POD1 were predictors for in-hospital mortality. It has been shown before that a high BMI is associated with worth outcome in ALF [21]. However, only the AST peak at POD1 and the labMELD POD1 were independently associated with the overall post-transplant survival. This finding indicates that preoperative recipient variables that reflect the preoperative health condition of the recipient affect the acute clinical course in the hospital. In turn, the overall time-dependent outcome seems to be a function of the injury/function of the transplanted graft, reflected by the increase in AST and the labMELD POD1 in this patient population. It has previously been shown that more severe graft injuries are associated with complications, including initial suboptimal graft function, ITBL, bile duct stenosis or graft fibrosis, and the need for retransplantation [22–25], thus influencing the survival of the patients.

The interpretation of the labMELD POD1 value may be affected by different parameters. The MELD score is determined by bilirubin, creatinine (dialysis) and INR. All of these parameters will be corrected after successful transplantation, depending on the preoperative kidney function (AKI or not), the amount of coagulation treatment (INR) and graft function, which indicates that labMELD POD1 qualifies as a marker for combined assessment for preoperative clinical condition and postoperative graft function. However, in patients with cholestatic liver diseases, a decrease of bilirubin to a normal range will take longer compared with other patients, which will affect the labMELD POD1. However, our cohort did not include patients who were transplanted for cholestatic diseases. The intraoperative median FFP transfusion rate was 7 units, which did not significantly affect the INR [26,27]. The median application of prothrombin complex concentrate (4 factor concentrate) was 0 units during LT, suggesting little impact on the INR as well. Therefore, utilization of the labMELD POD1 seems to be reasonable for our patient cohort for the indexed evaluation. This is in accordance to other studies which showed a relevant role of the postoperative MELD for other indications of liver transplantation, recently [28].

Other classifications, such as the concept of EAD, use values of INR and bilirubin later after transplantation [16]. However, this classification showed only a tendency to be associated with in-hospital mortality in univariable analysis but was not able to discriminate the outcome in the present data set. Interestingly, another well-accepted classification system, the DRI [29], failed to discriminate patients with a good prognosis from patients with a poor clinical course. It should be kept in mind that these scoring systems were designed to predict the outcome of overall populations. ALF accounts for 2–5% of liver transplant recipients in large databases [30] and approximately 5% in this study. The particularity of the studied population presumably explains the failure of these scoring systems.

The median DRI in this study was 1.6, which is similar to the overall median DRI in the Eurotransplant area [31]. This outcome reflects the ongoing organ shortage and subsequent use of reduced quality organs, even for the indication of ALF in Germany compared with other international regions (e.g., OPTN with a mean DRI of 1.3–1.4 [31,32]). A consecutive influence of this issue on overall survival has been discussed in detail elsewhere [33].

The strongest discriminator of patient survival after LT in our study was the preoperative pH. The majority of patients with a pH < 7.26 died after transplantation. However, this observation should be approached with caution, as all scoring systems are limited due to their positive and negative predictive values. Accordingly, the decision for LT, particularly for patients with ALF, should recognize all of the available clinical data, including age, amount of vasopressor support, coagulation treatment requirement, renal failure and concomitant diseases.

Indeed, an elaborate analysis of the objective assessment criteria for LT in the setting of ALF remains an issue of high interest [34]. Existing detailed studies have presented only small patient populations or analyzed highly specific subgroups [13]. Currently published ambitious registry data present a large patient population, which unfortunately underscores the restrictions of these data collections in terms of shallow parameters available for evaluation [5] like others before [14]. Hence, the presented factors in this study could offer auxiliary support in the risk evaluation by providing objective assessment criteria despite the aforementioned limitations.

As described by other authors [35], we divided the population into patients discharged alive and patients discharged deceased to assess the long-term survival after initial stabilization. Patients leaving the hospital alive demonstrated a nearly perfect follow-up with a 60-month survival of 92.5% (Fig. 2). The relevance of the initial clinical course for these patients after transplantation is underscored by this finding.

The present study has several limitations: it is a single-center study with a retrospective study design and only a limited number of patients. Pediatric transplants were excluded; thus, we were unable to comment on this cohort. The mean DRI was 1.6 in the present cohort, so a

comparison with patient cohorts representing lower donor risk indices should be approached with caution. Nonetheless, the present cohort demonstrates that compelling survival rates can be achieved despite utilization of these higher DRI organs.

Conclusion

The present study demonstrates the influence of the lowest pH before LT on in-hospital mortality after LT. Furthermore, the effect of the recipient BMI and the pH before LT on overall survival for patients undergoing LT for ALF is depicted. These factors may support the decision to perform a liver transplantation in the setting of acute liver failure. Nonetheless, the individual decisions for liver transplantation in the setting of ALF should follow bedside assessment and all available clinical data and their dynamics.

Authorship

DPH, MM, AP, FHS: participated in study design. DPH, MM, FHS: participated in data collection. DPH, FHS: participated in statistical analysis. DPH, AC, MH, AG, AP, FHS: participated in data interpretation. DPH, AG, AP, FHS: participated in manuscript preparation. DPH, AC, MH, AG, AP, FHS: participated in literature search.

Funding

The authors have declared no funding.

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