Quality in liver transplantation: perspectives on organ procurement and allocation

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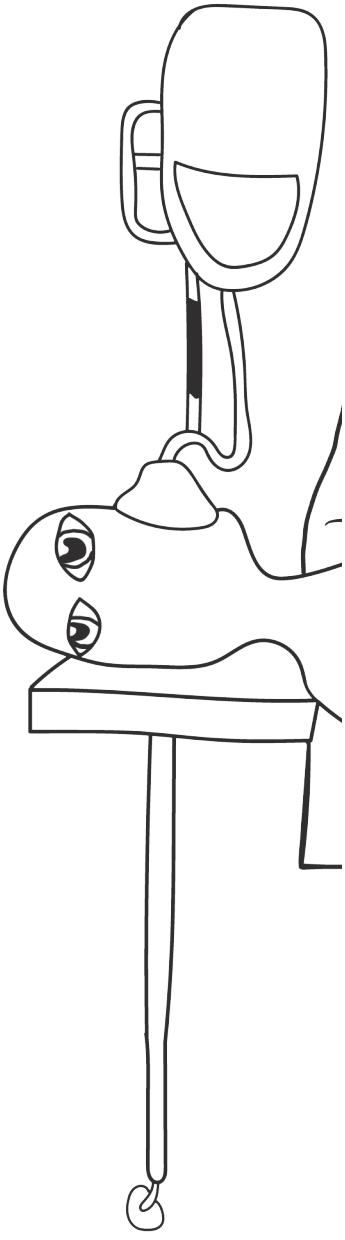

Chapter 8

Outcome of liver transplant patients with high urgent priority. Are we doing the right thing?

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On behalf of the Eurotransplant Liver and Intestine Advisory Committee (ELIAC)

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Abstract

Background
About 15% of liver transplantations (LTs) in Eurotransplant are currently performed in patients with a high-urgency (HU) status. Patients that have acute liver failure (ALF) or require an acute re-transplantation can apply for this status. This study aims to evaluate the efficacy of this prioritization.

Methods
Patients that were listed for LT with HU status from 01.01.2007 up to 31.12.2015 were included. Waiting list and posttransplantation outcomes were evaluated and compared with a reference group of patients with laboratory Model for End-Stage Liver Disease (MELD) score (labMELD) scores ≥40 (MELD 40+).

Results
In the study period, 2,299 HU patients were listed for liver transplantation. Ten days after listing, 72% of all HU patients were transplanted and 14% of patients deceased. Patients with HU status for primary acute liver failure showed better patient survival at 3 years (69%) as compared to patients in the MELD 40+ group (57%). HU patients with labMELD≥45 and patients with HU status for acute re-transplantation and LabMELD≥35 have significantly inferior survival at 3-year follow-up of 46% and 42%, respectively.

Conclusions
Current prioritization for patients with ALF is highly effective in preventing mortality on the waiting list. Although patients with HU status for ALF have good outcomes, survival is significantly inferior for patients with a high MELD score or for re-transplantations. With the current scarcity of livers in mind, we should discuss whether potential recipients for a second or even third re-transplantation should still receive absolute priority, with HU-status, over other recipients with an expected, substantially better prognosis after transplantation.

Introduction

Patients that present with acute liver failure (ALF) have a high risk of mortality because no bridging options are available for severe liver dysfunction. With the introduction of liver transplantation (LT) their chances for survival have increased significantly[1,2].

To increase the chance of a timely, suitable donor liver, 8 countries in Europe cooperate within Eurotransplant. This cooperation covers Germany, The Netherlands, Belgium, Austria, Croatia, Luxemburg, Hungary and Slovenia and has a total population of around 136 million inhabitants. Patients from these countries with primary ALF and patients that require an acute re-transplantation (<14 days) can apply for a 'high-urgency (HU)'-status[3]. The HU-status gives the patient international priority within all participating countries. When a suitable organ becomes available, HU patients are the first to receive an offer for that organ, cross border[3,4]. Patients can receive this status when they fulfill standard criteria or when accepted by an individual audit of two members of the Eurotransplant Liver and Intestine Advisory Committee (ELIAC) (Definitions; Methods[3]).

Over the last years (2012-2016), about 15% of all LTs within Eurotransplant were performed in patients with a HU-status[5]. HU status prioritization is currently considered justified because these patients are at imminent risk of death. It is primarily based on the urgency for LT but so far outcome of this allocation mode has been disregarded. The group of patients with HU status is heterogeneous and there might be a (sub) group of patients with very poor prognosis even in case of an urgent LT. These HU patients are currently transplanted with priority over other critically ill patients who face the risk of dying while on the waiting list, although they might have a significantly higher chance of survival.

This study aims to evaluate the efficacy of the high-urgent status on waiting list outcome. Then, outcome after LT is analyzed for transplanted HU patients to identify high-risk patients. These outcomes are compared to a reference group of patients without HU-status but with a MELD score of ≥40.

Methods

This study included anonymized data on all patients of 16 years and older, that were listed for LT with HU status within the Eurotransplant region, between January 1st, 2007 and December 31st, 2015. As a reference group, recipients most urgently in need for a transplantation but without HU status, were included. These recipients were defined as all patients that reached a laboratory MELD score (labMELD) ≥40, but without HU status.

Data were included on waiting list outcome and, in case of a transplantation, information on donor and transplant characteristics. This study considered transplantations instead of individual patients. Therefore, patients that receive multiple LTs may appear multiple times in the data. Follow-up data were obtained from the Eurotransplant Network Information System (ENIS) and the Eurotransplant Liver Follow up Registry up to 1st of February, 2018. The study protocol was approved by the Eurotransplant Liver Intestine Advisory Committee (ELIAC) and no ethical statement was required according to European guidelines and Dutch law.

Data analysis

The dataset contained donor information on age, sex, latest gamma-glutamyl-transpeptidase (GGT), Hepatitis C antibodies (HCVAb) status, Hepatitis B antibodies (HBcAb) status, type of donation (donation after determination of circulatory death(DCD)/ Donation after brain death (DBD)), cause of death, body mass index (BMI), history of diabetes (y/n), and recipient information on age at delisting, etiology of liver disease, BMI, HCVAb status, number of previous liver transplantations, labMELD category, sex, split (y/n), allocation region (local, regional, extra-regional), simultaneous liver and kidney (SLK), rescue allocation and total ischemic time.

Data were checked for outliers, and were set at missing or corrected when appropriate (length/weight switch). Recipient BMI was missing for one patient and donor last GGT was missing for 58 donors (0.02%). For both recipient BMI and donor last GGT median values were imputed; 25.4 and 32 U/l, respectively. Total ischemic time was defined as time between starting time of cold perfusion of the aorta in the donor and time of reperfusion in the recipient. In case of missing values (27 transplantations, 0.01%), median value of 8.35 hours was imputed. Donor hepatitis B antibodies, HCVAb and recipient HCVAb were considered as present when 'Yes' and not present when otherwise. Primary ALF diagnoses were categorized as 'Budd-Chiari', 'Viral hepatitis', 'Toxin/drug induced', 'Wilson's disease', 'paracetamol' and 'other'. Viral hepatitis comprised hepatitis A, B, C, D, E, Cytomegalovirus (CMV), herpes simplex virus (HSV) and other unspecified viruses. The category 'other' comprised etiologies as auto-immune diseases, post-operative liver failure, (liver) trauma, an-hepatic state, Osler's disease, Still's disease, Weil's disease, pregnancy related illnesses and alpha1-antitrypsin deficiency. Etiologies for acute re-transplantations were categorized as 'Hepatic artery thrombosis', 'Biliary tract necrosis', 'Portal vein thrombosis', 'Primary non function' and 'Other'. The 'Other' category comprised: acute cellular rejections, transmitted tumor in a recently transplanted liver, infected biliomas, other unspecified complications of the operation, rupture of a mycotic aneurysm, sinusoidal obstruction syndrome, ruptured and bad perfused organs, risk of tumor transmission, liver necrosis and compartment syndrome due to bleeding. For all transplantations the Eurotransplant-Donor Risk Index (DRI)[6], simplified Recipient Risk Index (sRRI)[7] and Donor and Recipient Model (DRM)[7] were calculated.

Definitions

HU and MELD 40+ groups

The HU-group consisted of patients suffering from primary ALF who fulfilled either King's College[8] or Clichy-Villejuif[9] criteria and patients that required an acute retransplantation for a primary graft non-function or hepatic artery thrombosis[3] (<14 days after LT) and patients not fulfilling standard HU criteria (e.g. acute Wilson's disease, Budd-Chiari syndrome with severe liver failure, life threatening liver trauma, anhepatic state secondary to ALF with toxic liver syndrome or patients who require an acute re-LT due to hepatic artery thrombosis >14 days post-transplantation) but were assigned HU status based on an individual audit. This audit is performed by at least two independent liver transplant surgeons and/or hepatologists being members of the ELIAC. The MELD 40+ group consisted of patients with a labMELD score ≥40 on the waiting list.

Outcome measures

Outcome after registration on the waiting list was defined as still on the waiting list, transplanted, deceased/unfit for transplantation ('mortality') or removed because of recovery or for other reasons (psychological problems). Outcome after transplantation was analyzed for patient survival. Patient survival was defined as the time period between transplantation and death of the recipient. Outcome was analyzed for patients that were transplanted within the follow-up period of this study (February 2018).

Statistical analysis

Waiting list outcome

Waiting list outcome was analyzed with a competing risk analysis for all patients that received HU status and all patients that reached a labMELD of 40 from the moment of either HU listing or from the moment of reaching labMELD 40. HU patients were considered as one group for this analysis because the HU status priority on the waiting list does not distinct between patients with primary acute liver failure and patients that require an acute re-transplantation.

Post-transplantation outcome

Patient survival at 3-year follow-up was analyzed for HU patients that were transplanted with a liver from a deceased donor (DBD or DCD type III) and compared to a homogenous reference group including MELD 40+ patients receiving the first liver transplant from a deceased donor (DBD or DCD type III). This analysis was done separately for patients receiving HU status for primary acute liver failure and for acute retransplantation.

Risk factors associated with patient survival at 3-year follow-up in HU patients were analyzed in a multivariable Cox-regression analysis (backward selection). This was also done separately for 1) patients with HU status for primary acute liver failure and for 2) patients with HU status for an acute retransplantation. On the basis of the distinct difference in outcome, patients with HU status for an acute-re-transplantation were

stratified for the number of previous liver transplantations. Then, outcome was analyzed separately for these groups by labMELD score category (<15, 15-24, 25-34, 35-44, ≥45). Last, outcome was analyzed by cause of liver disease for patients who received HU status for primary ALF and for patients that received HU status for an acute retransplantation after one previous LT.

Variables were summarized by median values and interquartile ranges (IQR) for continuous variables and by number and percentages (N/%) for categorical ones. Median values were compared with a Kruskal-Wallis tests and categorical variables were compared with Chi-square testing. Kaplan-Meier curves were analyzed by log-rank testing. A p-value of 0.05 was considered as statistically significant. Statistical analyses were performed with SPSS version 24 and R version 3.3.2.

Results

Waiting list

In the study period, 22,752 patients were registered on the liver waiting list. Of these patients, 2,299 received a HU status during listing (10%) (Figure 1). They had a median age of 49 years old and 48% were male. About half of these patients registered on the waiting list (47%) had a previous LT. Other demographics are shown in Table 1.

Waiting list outcome

At 10 and 30 days after listing, 72% and 74% of all HU patients were transplanted, respectively (Figure 2A, B). Waiting list mortality was 14% at 10 days, 15% at 30 days and increased up to 16% at 2-year follow-up. The transplantation rate for HU patients was significantly higher (75% vs. 51%, p<0.001) and waiting list mortality was significantly lower (18% vs. 48%, p<0.001) as compared to patients in the MELD 40+ group (n=1,580) (Figure 2B). When comparing not-transplanted (n=579, 25%) to transplanted HU patients (n=1,720, 75%), not-transplanted HU patients were older (51 vs. 49 years old, p=0.037). However, no statistically significant differences were observed in the labMELD score (32 vs. 32, p=0.638) or in the number of previous LTs (p=0.264) (data not shown).

Outcome after transplantation

In the study period, 1,719 transplanted HU patients were included for the analysis. In the reference group of patients with a labMELD score ≥40 at listing, 694 transplantations were included for the analysis. Of all transplanted patients with a HU status, 967 (56%) were patients with primary acute liver failure (ALF) while 752 (44%) were patients with a HU status for an acute retransplantation. In these HU patients (transplanted for failure of a previous transplantation), 651 (38%), 84 (5%) and 17 (0.1%) transplantations were performed in patients with 1, 2 or ≥3 previous LTs, respectively. Most frequent cause of primary ALF was toxic or idiosyncratic drugs (25%) followed by viral hepatitis

(13%), Budd-Chiari disease (9%) and other causes (40%). The other causes consisted of patients without a clear etiology (21%), other unspecified etiologies (14%), post-operative failure (3%), liver trauma (0.8%), an-hepatic state (0.7%) and one patient with urea cycle disorder (0.1%). In HU retransplantations, PNF (46%) was the most frequent cause for failure of the previous transplantation followed by an acute HAT (26%). The median recipient age in patients with 1, 2 or ≥3 previous LTs was 53, 48 and 34 years old, respectively. No difference in the cause of failure of the previous transplantation (etiology) was observed in these patient groups with 1, 2 or ≥3 previous LTs groups in the cause of failure of the previous transplantation (p=0.681). Other characteristics are shown in Table 2.

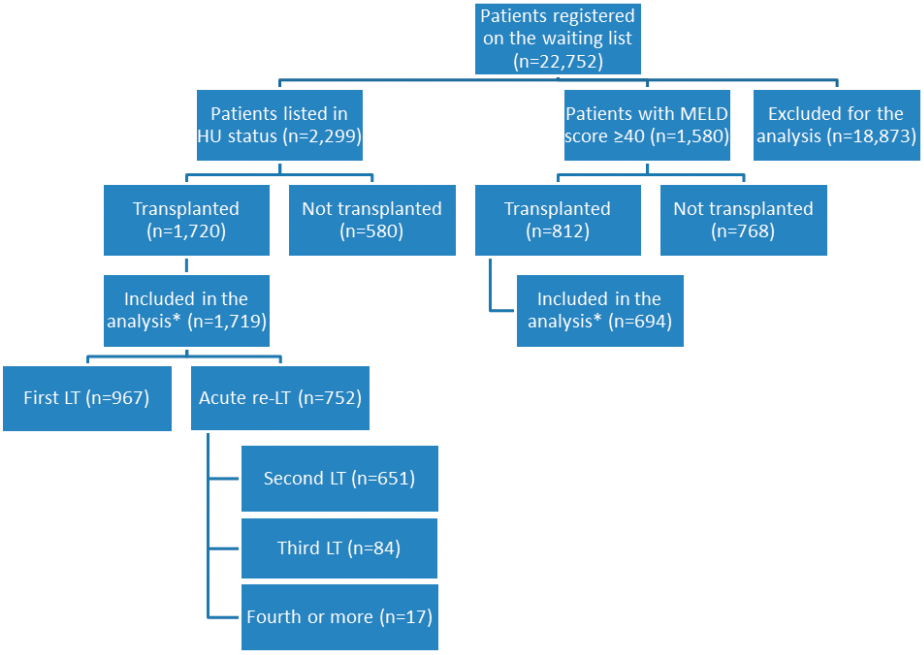

Figure 1. Flow diagram of patients listed for liver transplantation (LT). *Patients were included who were first time transplanted with a liver from a donation after brain death (DBD) and donation after determination of circulatory death (DCD) type III donor. HU, high urgency; MELD, Model for End-Stage Liver Disease.

Table 1. Demographics of patients listed in HU status (n=2,299)

Recipient factor	**n(%)/ Median (25th-75th percentile)**
Age at listing	49 (36-58)
Height (cm)	171 (165-178)
Weight (kg)	75 (65-86)
BMI	25 (22-28)
Lab-MELD at delisting	32 (24-38)
Sex (Male)	1101 (48)
Lab Meld at delisting	
<15	201 (9)
15 – 24	410 (18)
25 – 34	815 (36)
35-45	672 (29)
≥45	162 (39)
Missing	39 (2)
No. of previous liver transplants	
0	1,220 (53)
1	935 (41)
2	122 (5)
3	22 (1)
HCVAb (Yes)	153 (7)
sRRI	1.97 (1.56 - 2.62)
Waiting list outcome (10 days)	
Transplanted	72%
Deceased while on the WL	14%
Still on the waiting list	10%
Removed (unfit, recovered, other)	4%
Waiting list outcome (30 days)	
Transplanted	74%
Deceased while on the WL	15%
Still on the waiting list	5%
Removed (unfit, recovered, other	6%

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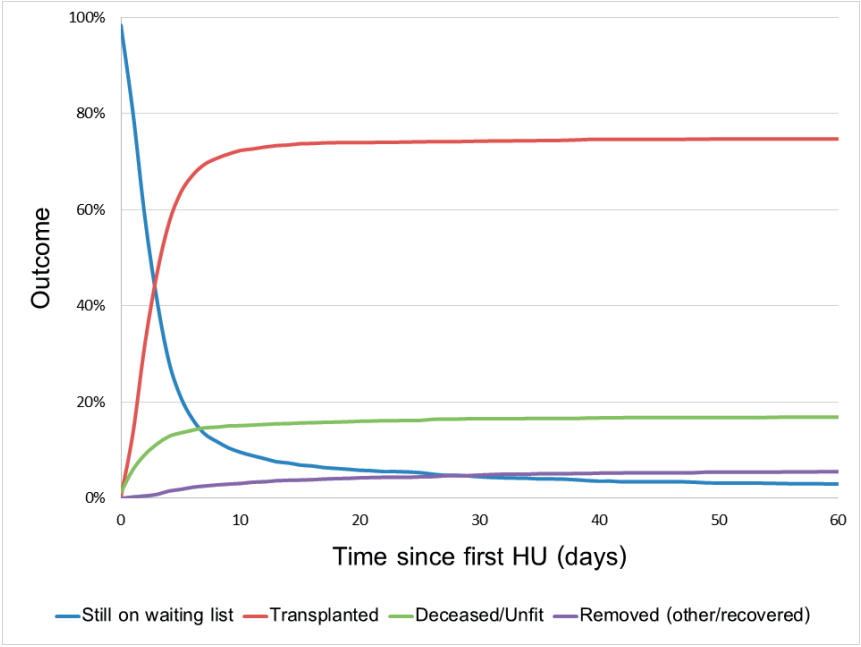

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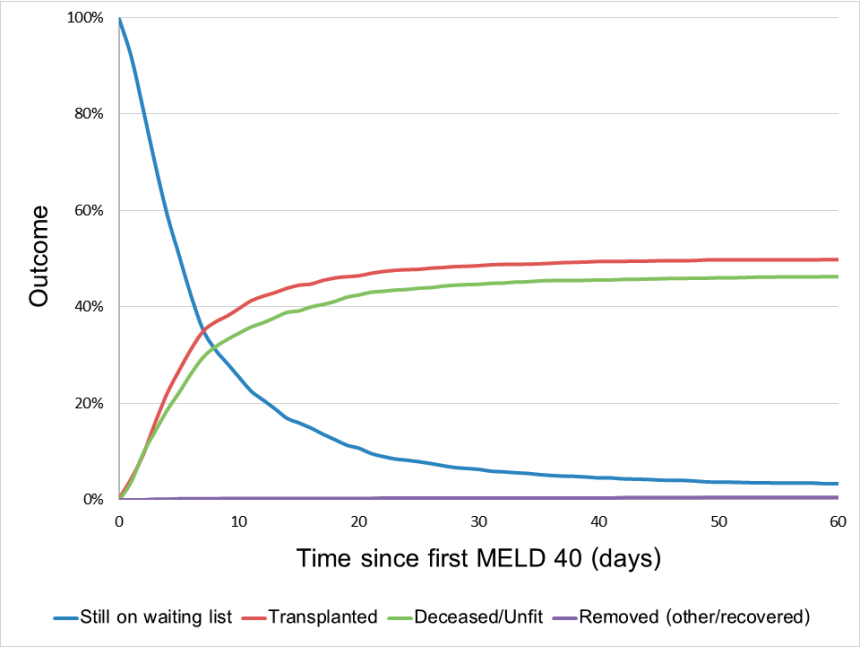


Figure 2. Waiting list outcome. A, Waiting list outcome of patients listed in high-urgency (HU) status. B, Waiting list outcome of patients listed with laboratory Model for End-Stage Liver Disease (MELD) score (labMELD) ≥40.

Table 2. Demographics of transplanted HU patients by number of previous liver transplantations (n=1,719)

	Primary acute liver failure (n=967)	**Acute re-transplantation after one previous LT (n=651)**	**Acute re-transplantation after two previous LTs (n=84)**	**Acute re-transplantation after three or more previous LTs (n=17)**
Recipient factor				
Age (years)	45 (33-55)	53 (45-60)	48 (40-55)	34 (25-46)
Height (cm)	170 (165-178)	173 (167-180)	173 (167-180)	175 (164-182)
Weight (kg)	75 (65-85)	78 (66-80)	72 (64-85)	63 (56-74)
BMI	25 (22-28)	26 (23-29)	24 (21-27)	22 (19-24)
Lab-MELD at transplantation	34 (28-39)	29 (21-35)	31 (25-36)	34 (23-36)
Dialysis while on the WL	149 (15)	237 (36)	43 (51)	7 (41)
Sex (Male)	372 (39)	408 (63)	49 (58)	9 (53)
HCVAb	19 (2)	92 (14)	12 (14)	0 (0)
Days between HU listing -and transplantation	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-4)
Days between listing and previous transplantation	n/a	5 (2-12)	7 (2-14)	8 (2-16)
Lab-MELD category at transplantation				
<15	57 (6)	69 (11)	6 (7)	0 (0)
15 – 24	97 (10)	187 (29)	15 (18)	5 (29)
25 – 34	374 (39)	228 (35)	34 (41)	6 (35)
35-44	336 (35)	145 (22)	28 (33)	6 (35)
≥45	92 (10)	17 (3)	1 (1)	0(0)
Missing	11 (1)	5 (1)	0(0)	0 (0)
Etiology acute liver failure				
Budd-Chiari	83 (9)			
Viral hepatitis	121 (13)			
Toxic or idiosyncratic drugs	238 (25)			
Wilson's disease	65 (7)			
Paracetamol	53 (6)			
Other	383 (40)			
Missing	24 (3)			
Etiology re-transplantation				

Table 2. Continued.

	Primary acute liver failure (n=967)	Acute re-transplantation after one previous LT (n=651)	Acute re-transplantation after two previous LTs (n=84)	Acute re-transplantation after three or more previous LTs (n=17)
HAT		169 (26)	23 (27)	7 (41)
ITBL		22 (3)	1 (1)	0 (0)
Other		84 (13)	14 (17)	1 (6)
PVT		26 (4)	2 (2)	0 (0)
PNF/DGF		299 (46)	41 (50)	8 (47)
missing		51 (8)	3 (4)	1 (6)
Donor factor				
Age (years)	49 (38-59)	48 (35-57)	47 (28-54)	52 (37-63)
Height (cm)	170 (165-180)	170 (165-180)	170 (165-179)	170 (165-178)
Weight (kg)	72 (65-80)	72 (65-80)	71 (64-80)	73 (67 - 80)
BMI	24 (23-26)	24 (22-26)	24 (22-26)	25 (22-28)
Last GGT (U/L)	32 (17-67)	30 (17-63)	31 (19-64)	46 (17-80)
Sex (male)	415 (43)	324 (50)	32 (38)	10 (59)
HCVAb (pos)	2 (0)	2 (0)	0 (0)	0 (0)
HBcAb (pos)	32 (3)	16 (3)	2 (2)	1 (6)
Donor type (DCD)	9 (1)	5 (1)	0 (0)	1 (6)
Split liver (yes)	30 (3)	15 (2)	0 (0)	2 (12)
Transplant factor				
Allocation				
Local	34 (4)	32 (5)	1 (1)	0 (0)
Regional	91 (9)	59 (9)	11 (13)	1 (6)
Extra-regional	842 (87)	560 (86)	72 (86)	16 (94)
Rescue (yes)	9 (1)	3 (1)	2 (2)	0 (0)
Cold ischemia time (hours)	8.37 (6.35-10.42)	7.85 (6.28 - 9.87)	8.02 (6.23-9.82)	7.00 (5.22-9.69)
Risk indices				
sRRI	2.62 (2.06-3.30)	1.67 (1.47-1.97)	1.58 (1.33-1.97)	1.56 (1.26-1.84)
ET-DRI	2.12 (1.80-2.39)	2.05 (1.74-2.34)	1.97 (1.73-2.30)	2.25 (2.02-2.68)
DRM	4.25 (3.12-5.42)	2.73 (2.19-3.42)	2.59 (2.14-3.20)	2.46 (2.21- 3.39)

Risk factors for posttransplant outcome in HU patients

Multivariable analysis of risk factors for patient survival at 3-year follow-up was performed in patients receiving HU status for primary ALF and for patients receiving HU status for an acute re-transplantation, separately (Table 3). In HU-patients with primary ALF the following risk factors were identified for poor patient survival; higher

donor age, split liver grafts, latest donor GGT, higher recipient age, etiology of acute liver failure, recipient BMI and the labMELD score. For HU retransplantations (n=752), the cause of graft failure of the previous liver transplantation, split liver grafts (n=17, 2%) and GGT had no statistically significant effect but the number of previous liver transplantations was associated with a higher risk of patient mortality.

Outcome by number of previous transplantations

Major differences in patient and graft survival were observed when posttransplantation outcome was stratified for patients receiving HU-status for primary ALF and those transplanted for failure of a previous transplantation by the number of previous LTs (Figure 3). Patient survival at 3 years decreased from 69% for HU patients with primary ALF, to 40-41% in HU patients with failure of the previous LT after ≥2 previous transplantations. Similar results were observed for graft survival (data not shown). Compared to the group of MELD 40+ patients, HU patients that were transplanted for primary ALF were observed to have a better survival at 90 days (80% vs. 76%, p=0.086), 1 year (73% vs. 63%, p<0.001) and at 3 years (69% vs 57%, p<0.001).

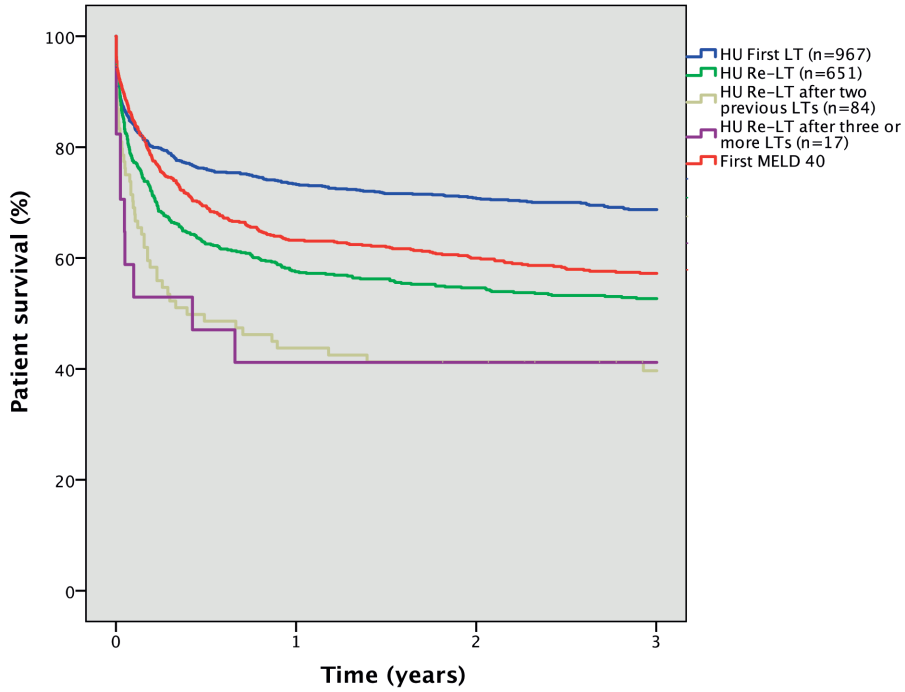


Figure 3. Posttransplantation outcome (patient survival) of high-urgency (HU) patients with primary acute liver failure (ALF), HU patients with failure of a previous liver transplantation (LT) by the number of previous transplantations and of first time transplanted Model for End-Stage Liver Disease (MELD) 40 patients.

Table 3. Multivariable analysis of factors associated with patient survival at 3- year follow-up in HU patients

	Patients with primary ALF (n=967)		**Patients after failure of a previous LT(n=752)**	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Donor				
Age (y)	1.010 (1.003-1.018)	0.010	1.008 (1.001-1.015)	0.033
Split (y)	2.242 (1.206-4.168)	0.011	NS	NS
latest GGT (U/L)	1.002 (1.000-1.003)	0.015	NS	NS
BMI	NS	NS	1.038 (1.005-1.073)	0.025
Recipient				
Age (y)	1.028 (1.019-1.038)	<0.001	1.011 (1.002-1.020)	0.017
Etiology of liver disease (Budd-Chiari)		0.009		
Viral hepatitis	1.270 (0.668-2.415)	0.466		
Toxin/drug induced	1.314 (0.726-2.378)	0.367	N/A	
Wilson's disease	1.091 (0.509-2.338)	0.822		
Other	1.870 (1.073-3.259)	0.027		
Paracetamol	0.870 (0.379-1.993)	0.741		
BMI	1.043 (1.020-1.068)	<0.001	NS	NS
Transplant				
Total ischemic time (continuos h)	NS	NS	1.057 (1.025-1.091)	<0.001
Number of previous LTs (1)	N/A			0.013
2			1.474 (1.075-2.020)	0.016
≥3			1.877 (0.982-3.587)	0.057
Meld category (<15)		<0.001		<0.001
15-25	1.068 (0.586-1.949)	0.829	1.369 (0.851-2.200)	0.195
25-35	0.849 (0.495-1.458)	0.554	2.018 (1.282-3.177)	0.002
35-45	0.698 (0.401-1.215)	0.204	2.494 (1.568-3.968)	<0.001
≥45	2.045 (1.131-3.696)	0.018	1.744 (0.745-4.087)	0.200

Not significant in multivariable analysis backward selection (Wald): Donor sex, HCVAb, HBcAb, Cause of death donor, Allocation region, TIT, Diabetes, Days between HU and TX, DCD, Kidney combination, Rescue allocation and Recipient HCVAb. * For missing data for one of the variables, 35 of all 967 patients with primary acute liver failure and 60 of all 752 acute re-transplantations were excluded for this analysis.

The effect of labMELD score on outcome in HU patients

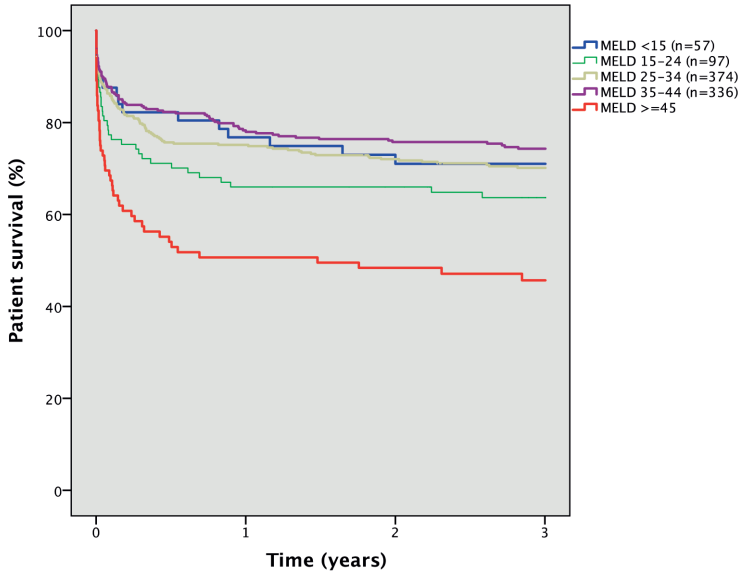
LabMELD score as continuous variable was strongly associated with outcome in HU patients (Figure S1). The effect on 3-years patient survival was non-linear in patients receiving HU status for primary acute liver failure: it shows a stable risk up to a score of about 40 after which it increases linearly at least up to a labMELD score of 55 (Figure S1a). The nonlinear association of a continuous labMELD score in this group may be caused by differences in the etiology of ALF within the labMELD score categories; some of the causes might not result in a high labMELD score. A relatively higher incidence of Budd-Chiari disease was for example observed in patients with a labMELD score below 15 (33%) and between 15 and 24 (20%) as compared to 7%, 4%, 2% in patients with a labMELD score of 25-34, 35-44 and ≥45, respectively. In HU patients who were retransplanted for failure of the previous LT (one previous LT), labMELD score did show a linear association (Figure S1b).

Outcome by labMELD and number of re-transplantations in HU patients

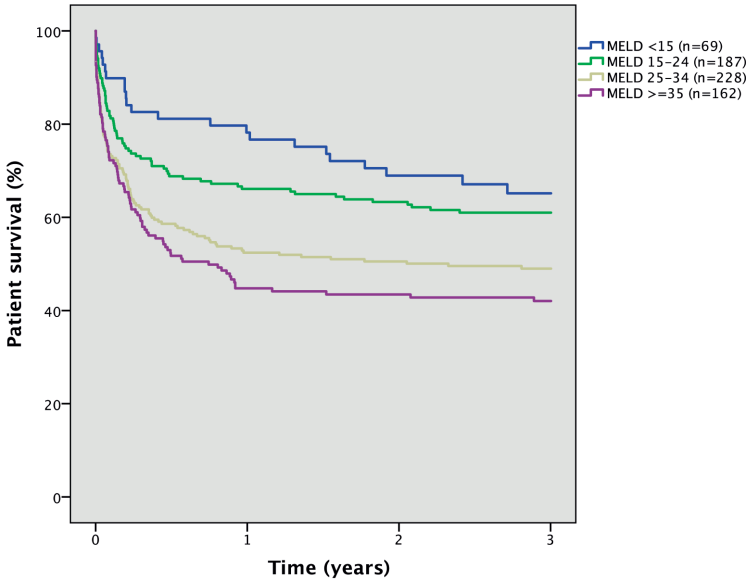
Outcome was then stratified for labMELD score and the number of previous LTs in a subset analysis (Figure 4). The combination of both variables was very effective in identifying subgroups with inferior outcome. It showed that patients receiving HU status for primary ALF with a labMELD score ≥45 had a survival rate of 46% at 3 years (Figure 4a). HU patients that were retransplanted after failure of ≥1 previous LT(s) and who had a labMELD score ≥35 had a survival rate of less than 42% at 3 years after transplantation (Figure 4b-d).

Outcome of transplanted HU patients by diagnosis

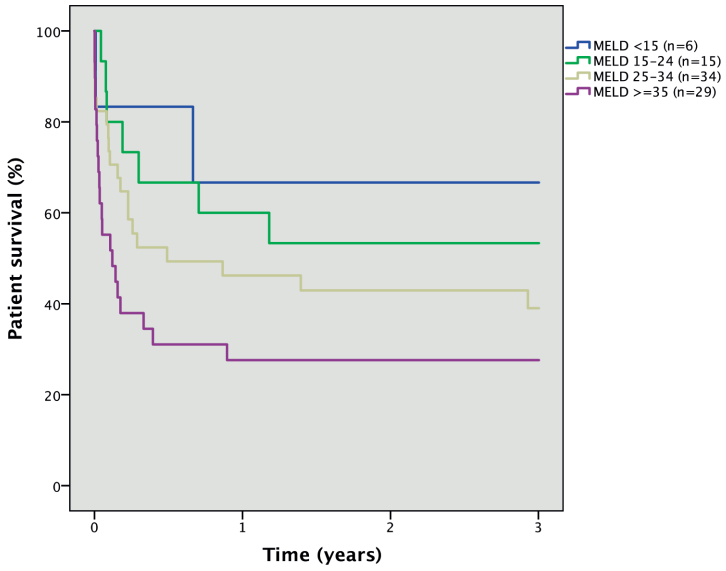
Significant differences in patient survival were observed for patients receiving HU status for primary ALF by the cause of the ALF ($p<0.001$) (Figure 5a). Patients listed for Budd-Chiari, paracetamol intoxication and Wilson's disease showed a trend towards better patient survival as compared to patients presenting with liver failure induced by toxin and/or drugs or viral infections. Although the median period from listing to transplantation was 2 days in all groups, statistically significant differences were present between the groups (<0.001). Patients with Budd-Chiari had the longest mean time period between listing and LT (3.4 days). In patients with HU status for failure of the previous LT (1 previous LT), those with an acute HAT(n=167) show better patient survival as compared to patients with a PNF (n=299) at 1 year (66% vs. 52%, $p=0.007$) and at 3-year follow-up (62% vs. 49%, $p=0.009$). The difference in survival at 90 days of 73% vs. 66% was not statistically significant ($p=0.118$), Figure 5b. When compared with PNF patients, HAT patients were observed to have a longer median time period between the previous LT to re-listing (8 days (3-14) vs. 2 days (1-8), $p<0.001$) and a trend for longer median time period between the re-listing in HU status and re-transplantation (2 days (1-4) vs. 2 days (1-3), $p=0.078$).


Patient survival (%)
100
80
60
40
20
0
0
1
2
3
Time (years)
MELD <15 (n=57)
MELD 15-24 (n=97)
MELD 25-34 (n=374)
MELD 35-44 (n=336)
MELD >=45

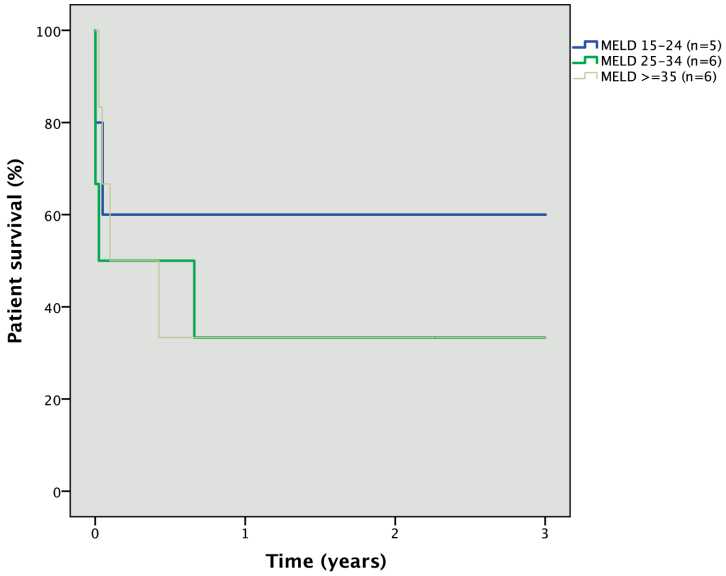
A.


Patient survival (%)
100
80
60
40
20
0
0
1
2
3
Time (years)
MELD <15 (n=69)
MELD 15-24 (n=187)
MELD 25-34 (n=228)
MELD >=35 (n=162)

B.

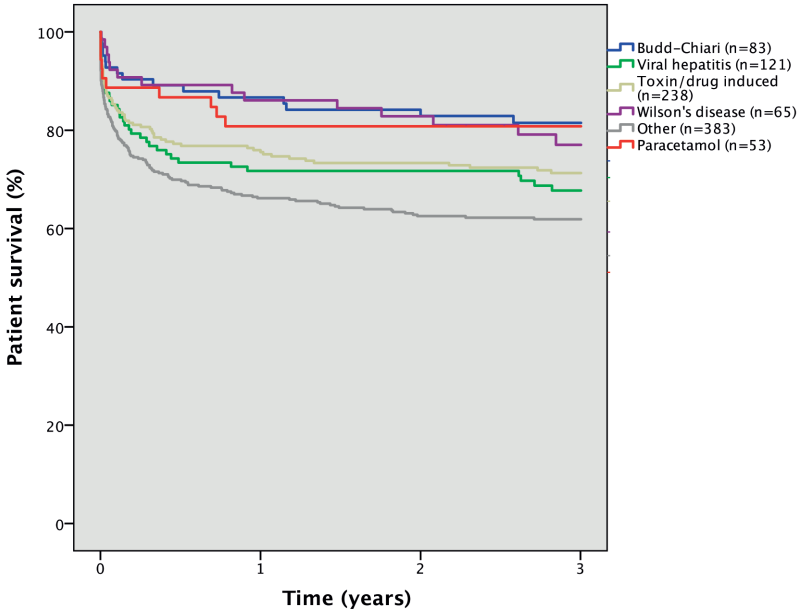


C.

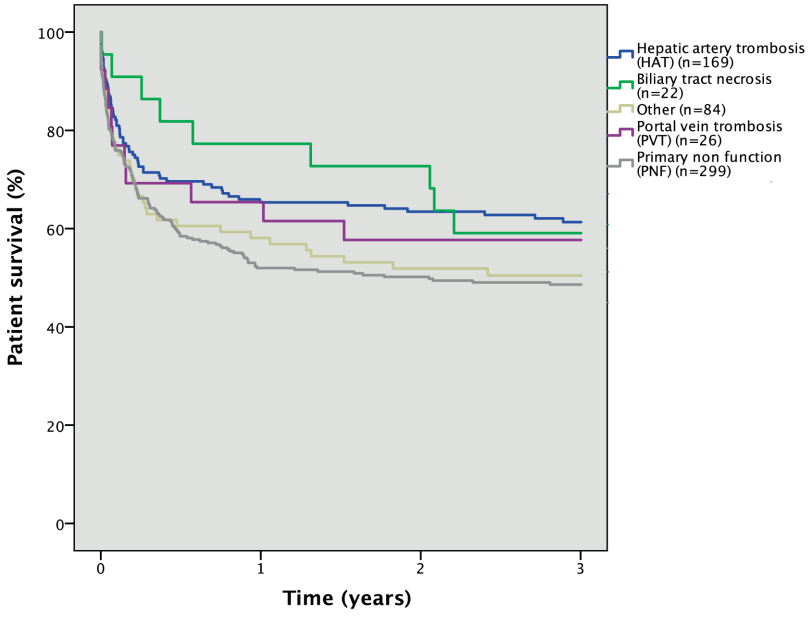


D.

Figure 4. Posttransplantation outcome (patient survival) of high-urgency (HU) patients by laboratory Model for End-Stage Liver Disease (MELD) score category and number of retransplantations. A, HU patients with primary acute liver failure (ALF; n = 967). B, HU retransplantations with 1 previous liver transplantation (LT; n = 651). C, HU retransplantations with 2 previous LTs, n = 84. D, HU retransplantations with ≥3 previous LTs, n = 17.



A.



B.

Figure 5. Posttransplantation outcome (patient survival) of high-urgency (HU) patients by cause. A, Patient survival of HU patients with primary acute liver failure (ALF). B, Patient survival of HU retransplantations after 1 previous transplantation by cause.

Discussion

This study shows that the current HU prioritization is highly effective to transplant patients with ALF or that require an acute retransplantation within days. However, because of the prioritization for HU patients, other patients are disadvantaged. Transplanting these high-risk patients therefore represents an important dilemma in which interests of individual patients compete with interests of all patients on the waiting list, as a group[10]. This dilemma is even more important in a context of scarcity of transplantable livers and a substantial waiting list mortality in the Eurotransplant region.

Post-transplantation outcomes are currently not taken into account in the allocation algorithm for livers within the Eurotransplant region[4]. Especially for the HU prioritization, current criteria focus primarily on identifying patients who will die without a transplantation and there is no distinction by prognosis[8,9]. Although results from this study show that the majority of patients with HU status for primary ALF have better outcomes than MELD 40 patients, some (substantial) groups of HU patients have not. Nevertheless, these HU recipients (retransplantations or patients or with a very high MELD score) receive absolute priority over other 'regular' patients despite their inferior post-transplantation survival. Even when these other patients are in an urgent need for a transplantation (as reflected in a LabMELD score ≥40).

Based on the inferior outcomes it has been suggested before to limit the maximum number of LTs[11–16]. We feel that such absolute guidelines would not be favorable as the clinical evaluation of individual patients remains important and exceptions should still be possible. Another suggestion would be to reconsider the *absolute* priority of all HU patients over non-HU recipients. Sharma *et al.* stated in 2012 that based on the higher waiting list mortality and better post-transplant outcome, MELD-40+ patients should be assigned higher priority than patients with Status-1A[17]. Based on our results that would not apply to all, because HU patients with primary acute liver failure have better outcomes than MELD 40+ recipients. It could, however, apply to HU patients with primary acute liver failure and a MELD score ≥45 and/or for patients with HU status for an acute re-transplantation after one or more previous LTs and a MELD score ≥35 who have a survival rate at 3 years of 46% and 42%, respectively. It might therefore be justified to differentiate within the absolute priority of HU status. On the basis of the (major) differences in outcome, patients with two or more previous liver transplantations might, for example, receive only national priority (instead of international priority), or only extra exception MELD-points. But most important, knowledge and education about outcome of such patients is critical and there is a key-role for the treating physician and transplant center. With this knowledge, a critically

evaluation should be done whether such patients are to be relisted and subsequently receive a (scarce) liver over other very ill patients on the waiting list.

Significant differences in waiting list outcome are observed when comparing outcome for patients listed for emergency liver transplantation in Eurotransplant to other transplantation organizations. For example, when waiting list outcome of HU patients in Eurotransplant is compared to status-1 or the later status 1-A in the US[18]. Kremers *et al.* analyzed 720 patients listed in status-1 in 2004. Of these, 46% were listed for an acute retransplantation (47% in this study). Of all status-1 patients, 56% were transplanted and 13% had died 30 days after listing[19]. Sharma *et al.* compared waiting list mortality after 14 days between patients with a MELD-score ≥40 with patients listed in status-1A status in 2012[17]. They observed a 14 days' waiting list mortality of about 50% in patients with a MELD score ≥40 and of 30% for patients with status-1A. Within Eurotransplant a higher proportion of the high-urgent patients is transplanted in a shorter period of time (72% after 10 days), while waiting list mortality (15%) is about similar or lower. Our results are more comparable to patients listed with a super-urgent status in France[20] and patients listed for emergency liver transplantation in the UK[2]. They report a waiting list mortality of 14% and 17% and a transplant rate of 73% and 76% in France and the UK, respectively.

The observed post-transplantation outcomes for first time transplanted patients with ALF of 75% and 72% at 1 and 3 years, are in accordance with other studies. In comparing results, it is of note that although most patients with primary ALF included in this study fulfill either King's or Clichy-Villejuif's criteria for acute liver failure, many patients were accepted for HU status by an expert panel of the Eurotransplant liver committee. Although this might be a potential limitation for comparing outcome with other regions and/or databases, this is the current practice within the Eurotransplant region. Other studies have a reported patient survival that varies from 69% to 81% at 1 year and from 64% to 78% at 3 years' follow-up[2,14,15,17,21–23]. Results on outcome after acute retransplantations are more scarce. Post-transplantation survival is reported to vary from 54% to 75% at one year and from 49% to 67% after 3 years[13,14,16,24,25]. In these patients, the time period between the first and second transplantation[11,24] and the reason for re-transplantation[25] are reported to have an important effect on outcome. Survival at 30 days after retransplantations was, for example, reported to be over 90% for HAT while patients with a PNF seem to do a lot worse with survival around 80%[19]. Better outcome for patients with HAT as compared to PNF was also observed in our study. It is however, interesting to see that the distribution of re-transplantation indication differs significantly[11,14]. The observation that outcome decreases with an increasing number of previous LTs is confirmed by studies from the US and data from the European Liver Transplant Registry (ELTR)[12,14,15]. It would be furthermore of interest to see whether livers from DCD donors may be used for urgent liver (re-)

transplantations. In this dataset, such transplantations were scarce and limited a more detailed analysis.

Our results reflect the struggle between the interest of individual patients and all patients on the waiting lists as a whole. The absolute priority of the HU status is now applied to a heterogeneous group of patients with primary ALF or with failure of previous LT(s) and other patients are therefore disadvantaged. To achieve a fair balance between HU and elective patients, the granting of HU status should be based on the actual waiting list mortality and the chances of success of the transplantation. Until that moment, HU requests should be critically evaluated by the community and, in times of organ scarcity, only be requested for patients with an acceptable prognosis when transplanted.

Conclusions

The prioritization for patients with ALF is highly effective in preventing mortality on the waiting list. Patients with HU status for primary ALF have a relatively high patient survival that exceeds survival of other seriously ill patients (for example those with a MELD score of 40+) or patients that have HU status for a (acute) re-transplantation. With the current scarcity of livers in mind, it has to be discussed whether recipients should still be prioritized for a second or even third retransplantation over other potential recipients who have a much better prognosis after transplantation.

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References

1. O'Grady J. Timing and benefit of liver transplantation in acute liver failure. *J Hepatol*. 2014;60(3):663-670. doi:10.1016/j.jhep.2013.10.024.
2. Bernal W, Cross TJS, Auzinger G, et al. Outcome after wait-listing for emergency liver transplantation in acute liver failure: A single centre experience. *J Hepatol*. 2009;50(2):306-313. doi:10.1016/j.jhep.2008.09.012.
3. Eurotransplant. Chapter 5 - ET Liver Allocation System (ELAS). *Eurotransplant Man*. 2018;February(Liver allocation). https://www.eurotransplant.org/cms/index.php?page=et_manual.
4. Jochmans I, Van Rosmalen M, Pirenne J, Samuel U. Adult Liver Allocation in Eurotransplant. *Transplantation*. 2017;101(7):1542-1550. doi:10.1097/TP.0000000000001631.
5. Eurotransplant International Foundation. *Annual Report 2016*. Eurotransplant International Foundation; 2016. www.eurotransplant.org.
6. Braat AE, Blok JJ, Putter H, et al. The eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant*. 2012;12(10):2789-2796. doi:10.1111/j.1600-6143.2012.04195.x.
7. Blok JJ, Putter H, Rogiers X, et al. Combined Effect of Donor and Recipient Risk on Outcome After Liver Transplantation: Research of the Eurotransplant Database. *LIVER Transplant*. 2015;21(12):1486-1493. doi:10.1002/lt.24308.
8. O'Grady J, Alexander G, Hayllar K, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology*. 1989;97(2):439-445.
9. Bernuau J, Goudeau A, Poynard T, et al. Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology*. 1986;6(4):648-651.
10. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. *Am J Transplant*. 2008;8(2):419-425. doi:10.1111/j.1600-6143.2007.02086.x.
11. Marudanayagam R, Shanmugam V, Sandhu B, et al. Liver retransplantation in adults: A single-centre, 25-year experience. *Hpb*. 2010;12(3):217-224. doi:10.1111/j.1477-2574.2010.00162.x.
12. Memeo R, Laurenzi A, Pittau G, et al. Repeat liver retransplantation: Rationale and outcomes. *Clin Transplant*. 2016;30(3):312-319. doi:10.1111/ctr.12691.
13. Akpinar E, Selvaggi G, Levi D, et al. Liver retransplantation of more than two grafts for recurrent failure. *Transplantation*. 2009;88(7):884-890. doi:10.1097/TP.0b013e3181b6f20e.
14. Adam R, McMaster P, O'Grady JG, et al. Evolution of liver transplantation in Europe: Report of the European Liver Transplant Registry. *Liver Transplant*. 2003;9(12):1231-1243. doi:10.1016/j.lts.2003.09.018.
15. Busuttil RW, Farmer DG, Yersiz H, et al. Analysis of long-term outcomes of 3200 liver transplantations over two decades: A single-center experience. *Ann Surg*. 2005;241(6):905-918. doi:10.1097/01.sla.0000164077.77912.98.
16. Azoulay D, Linhares MM, Huguet E, Delvart V, Castaing D, Adam R et al. Decision for Retransplantation of the Liver. *Ann Surg*. 2002;236(6):713-721. doi:10.1097/01.SLA.0000036264.66247.65.
17. Sharma P, Schaubel DE, Gong Q, Guidinger M, Merion RM. End-stage liver disease candidates at the highest model for end-stage liver disease scores have higher wait-list mortality than status-1A candidates. *Hepatology*. 2012;55(1):192-198. doi:10.1002/hep.24632.
18. U.S. Department of Health and Human Services. OPTN Policy 9: Allocation of livers and liver-intestines. https://optn.transplant.hrsa.gov/resources/by-organ/liver-intestine/. Accessed June 28, 2018.
19. Kremers WK, Van Ijperen M, Kim WR, et al. MELD Score as a Predictor of Pretransplant and Posttransplant Survival in OPTN/UNOS Status 1 Patients. *Hepatology*. 2004;39(3):764-769. doi:10.1002/hep.20083.

20. Ichai P, Legeai C, Francoz C, et al. Patients with acute liver failure listed for superurgent liver transplantation in France: reevaluation of the Clichy-Villejuif criteria. *Liver Transpl*. 2015;21(4):512-523. http://onlinelibrary.wiley.com/doi/10.1002/lt.24092/full. Accessed August 19, 2016.
21. Germani G, Theocharidou E, Adam R, et al. Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. *J Hepatol*. 2012;57(2):288-296. http://www.sciencedirect.com/science/article/pii/S0168827812002723. Accessed August 19, 2016.
22. Roberts MS, Angus DC, Bryce CL, Valenta Z, Weissfeld L. Survival after liver transplantation in the United States: A disease-specific analysis of the UNOS database. *Liver Transplant*. 2004;10(7):886-897. doi:10.1002/lt.20137.
23. Rodriguez Lopez M, Perez Saborido B, Pacheco Sanchez D, et al. Transplantation for Acute Liver Failure: Report of Results in the Region of Castilla y Leon (Spain) After 10 Years of Activity. *Transplant Proc*. 2012;44(9):2625-2626. doi:10.1016/j.transproceed.2012.09.042.
24. Rana A, Petrowsky H, Kaplan B, et al. Early liver retransplantation in adults. *Transpl Int*. 2014;27(2):141-151. doi:10.1111/tri.12201.
25. Postma R, Haagsma EB, Peeters PMJG, Van Den Berg AP, Slooff MJH. Retransplantation of the liver in adults: Outcome and predictive factors for survival. *Transpl Int*. 2004;17(5):234-240. doi:10.1111/j.1432-2277.2004.tb00436.x.