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Retransplantation in Late Hepatic Artery Thrombosis: Graft Access and Transplant Outcome

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Background. Definitive treatment for late hepatic artery thrombosis (L-HAT) is retransplantation (re-LT); however, the L-HAT–associated disease burden is poorly represented in allocation models. **Methods.** Graft access and transplant outcome of the re-LT experience between 2005 and 2016 was reviewed with specific focus on the L-HAT cohort in this single-center retrospective study. **Results.** Ninety-nine (5.7%) of 1725 liver transplantations were re-LT with HAT as the main indication (n = 43; 43%) distributed into early (n = 25) and late (n = 18) episodes. Model for end-stage liver disease as well as United Kingdom model for end-stage liver disease did not accurately reflect high disease burden of graft failure associated infections such as hepatic abscesses and biliary sepsis in L-HAT. Hence, re-LT candidates with L-HAT received low prioritization and waited longest until the allocation of an acceptable graft (median, 103 days; interquartile range, 28-291 days), allowing for progression of biliary sepsis. Balance of risk score and 3-month mortality score prognosticated good transplant outcome in L-HAT but, contrary to the prediction, the factual 1-year patient survival after re-LT was significantly inferior in L-HAT compared to early HAT, early non-HAT and late non-HAT (65% vs 82%, 92% and 95%) which was mainly caused by sepsis and multiorgan failure driving 3-month mortality (28% vs 11%, 16% and 0%). Access to a second graft after a median waitlist time of 6 weeks achieved the best short- and long-term outcome in re-LT for L-HAT (3-month mortality, 13%; 1-year survival, 77%). **Conclusions.** Inequity in graft access and peritransplant sepsis are fundamental obstacles for successful re-LT in L-HAT. Offering a graft for those in need at the best window of opportunity could facilitate earlier engrafting with improved outcomes.

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Organ replacement by liver transplantation (LT) has evolved over the past half century into the standard therapy for advanced liver failure. European transplant activity attained an impressive 93 634 liver engraftments between May 1968 and December 2009 with a peak annual transplantation rate of 5956 organs in 2007.[1] The overall benefit of LT has been clearly demonstrated with 1-year graft survival ranging between 70% and 83% depending on primary transplant indication. The salvage of recipients with a failing liver graft by a second organ reportedly accounts for 8.8% of the total transplant volume[1,2]; however, liver retransplantation (re-LT) yields inferior results than the first transplant with a 1-year graft survival of 57% and has therefore been identified as a strong negative predictor in transplant outcome.[1,3]

Hepatic artery thrombosis (HAT) is the most common indication for re-LT. The overall incidence of HAT has been reported in up to 9% of adult liver recipients with one third occurring early and the remainder manifesting late after LT.[4] Between half and two third of the early HAT (E-HAT) patients lose their graft as urgent revascularization with thrombectomy, revision of anastomosis, or thrombolytic

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drug therapy has limited success.[5,6] Late HAT (L-HAT) may be conservatively managed if sufficient arterial collateralization develops; yet, the majority of L-HAT grafts develop ischemic cholangiopathy (IC) necessitating rescue re-LT.[4]

The objective of this study was to assess the contemporary state of re-LT with a specific focus on listing management and transplant outcome in L-HAT at a high-volume center in the United Kingdom. Furthermore, we characterized the prototypical clinical spectrum of L-HAT and assessed the predictive value of tools to measure disease burden, such as model for end-stage liver disease (MELD) as well as United Kingdom model for end-stage liver disease (UKELD), and to predict transplant outcome with utility-based survival models, such as balance of risk (BAR) score and 3-month mortality score. This formed the basis to evaluate graft selection and graft access for L-HAT re-LT candidates under a center-based allocation policy.

MATERIALS AND METHODS

Study Design

All adult recipients of cadaveric LT that were transplanted consecutively from January 1, 2005, until March 31, 2016, at the Queen Elizabeth Hospital Birmingham (n = 1725) were included in this study, which was approved by the Institutional Clinical Audit and Research Management System (CARMS-11808). Re-LT candidates were relisted based on the decision of a weekly multidisciplinary transplant meeting. Center-based organ allocation allowed for optimal matching of urgency-driven or UKELD-guided recipient prioritization and acceptable graft quality. Technical aspects of the retransplant procedure were standard with a liberal use of infrarenal transmesocolic arterial interposition conduits. Most data were extracted from the prospectively maintained transplantation database, and the data collection of additional parameters was completed in a retrospective manner.

Subgroups were formed according to indication for a second graft and elapsed time after de novo transplantation (early re-LT defined as regraft within 21 days; late re-LT defined as regraft beyond 21 days).[4] Re-LT for HAT was compared with all other indications including primary nonfunction, sepsis, chronic rejection, HCV recurrence, ischemic type biliary lesions, and other liver specific or nonspecific causes of graft failure. Subgroups were analyzed for donor and recipient demographics, transplant interval morbidity, listing details, graft choice, surgical details, and retransplant outcome including graft function and survival. Specific to L-HAT retransplant candidates, the nadir in early mortality and the peak in 1-year survival was calculated based on progressive waitlist time and the median waitlist time for this optimized outcome was determined.

HAT Diagnosis

Doppler ultrasound was performed on demand based on clinical pattern or routinely in high-risk patients with complex arterial reconstruction of the liver graft. Absent arterial inflow was alarming and definitive diagnosis of HAT was confirmed by CT angiography. A minority of E-HAT patients underwent early revascularization with a reported success rate of 75%; however, interventional or surgical revascularization attempts were deemed futile in L-HAT based on the assumption that the thrombotic event was longstanding.[4]

Statistical Analysis

The results are expressed as percentage or median with interquartile range. Graft and patient survival data are plotted as Kaplan-Meier curves. Multivariable data analysis was performed by 2-tailed χ^2 test or Fisher exact test with 95% confidence interval for categorical parameters, Kruskal-Wallis test with Dunn post hoc adjustment for continuous variables and Mantel-Cox log-rank test for survival data (Prism V5.01; GraphPad, San Diego, CA). A probability level of P less than 0.05 was considered statistically significant.

RESULTS

Re-LT Indications and Graft Characteristics

Re-LT was performed in 99 recipients resulting in an average re-LT rate of 5.7% during the 11-year study period. Re-LT for E-HAT was necessary in 25 patients, whereas 18 patients underwent re-LT for L-HAT, accounting together for 43% of all second engraftments. Non-HAT indications resulted in equal numbers of early and late re-LT (n = 28 each). De novo liver transplant recipients that later developed E-HAT were more likely to be female (n = 20; 80%), whereas late non-HAT diagnosis was made in a significantly younger patient population (35 [24-43] years) than other subgroups. All other analyzed recipient, donor, and transplant characteristics of the first graft remained insignificant among the subgroups (Table 1).

Median first graft survival was 3 (2-6) days for early non-HAT, 12 (7-16) days for E-HAT, 1073 (142-1969) days for late non-HAT, and 582 (85-1264) days for L-HAT. Re-LT candidates with early non-HAT had significantly higher MELD, whereas L-HAT patients notably scored the lowest MELD before re-LT (Table 2). These differences were less evident albeit still significant for the UKELD scores. Further details on transplant indication, graft choice and technical aspects of the second grafts are given in Table 2.

Inequity in Graft Access for L-HAT Patients

E-HAT patients were rapidly relisted on the day of HAT diagnosis (median 0 [0-1] days), whereas listing for a second graft in L-HAT was highly significant delayed with a median of 10 (0-34) days. The time lag between HAT diagnosis and re-LT was even greater. The median time to re-LT from the time of diagnosis and listing in L-HAT was 139 (39-310) days and 103 (28-291) days, respectively (Figure 1B). In the contrary, E-HAT patients were retransplanted within a median of 3 (0-9) days, and this was in keeping with the graft access policy in the United Kingdom. Fast access to good grafts in early re-LT was granted through eligibility of super-urgent listing status, which is generally not accessible for L-HAT and late non-HAT patients. As a result, L-HAT re-LT candidates waited longest for their second liver graft (Figure 1A).

Frequent Intrahepatic Morbidity and Hospitalization in L-HAT Patients Awaiting Re-LT

Late non-HAT and L-HAT patients experienced similar cumulative systemic complications with a Clavien grade 3 or higher during the transplant interval between their first and second graft (Figure 2A). Yet, the full spectrum of

intrahepatic complications with IC, bilioma formation, hepatic abscess, and biliary sepsis necessitating biliary interventions was significantly more pertinent to L-HAT patients (Figure 2B). This biliary disease prompted a large amount of hospital readmission days in L-HAT similar to hospital readmissions of late non-HAT patients for parenchymal graft failure with hepatic encephalopathy or ascites (32 [8-66] vs 31 [11-52] days).

TABLE 1.

Recipient, donor, and graft characteristics of de novo liver transplant

	Entire cohort	Early non-HAT	Early HAT	Late non-HAT	Late HAT	*P*
Number	99 (99)	28 (28)	25 (25)	28 (28)	18 (18)	
Recipient						
Age, y	46.3 (35-56)	54.1 (39-60)	48.5 (44-60)	35.3 (24-43)	49.8 (42-56)	<0.001
Sex						
Male	45 (46)	17 (61)	5 (20)	16 (57)	7 (39)	
Female	54 (54)	11 (39)	20 (80)	12 (43)	11 (61)	0.026
MELD	17 (11-23)	17 (10-24)	18 (14-21)	16 (13-25)	19 (9-24)	0.996
UKELD	55 (50-61)	55 (50-61)	54 (50-60)	55 (52-61)	54 (49-62)	0.988
BMI	25.6 (23-29)	26.2 (24-30)	23.7 (22-27)	25.9 (23-30)	26 (23-29)	0.268
Primary liver disease						0.882
Acute liver failure	20 (20)	5 (18)	3 (12)	8 (29)	4 (22)	
Cholestatic disease	32 (32)	4 (14)	9 (36)	12 (43)	7 (39)	
Viral hepatitis	15 (15)	6 (21)	3 (12)	3 (11)	3 (17)	
Nonviral cirrhosis	26 (26)	12 (43)	7 (28)	3 (11)	4 (22)	
Primary non-HCC tumor	1 (1)	0 (0)	0 (0)	1 (4)	0 (0)	
Metabolic	1 (1)	0 (0)	1 (4)	0 (0)	0 (0)	
Budd-Chiari	2 (2)	1 (4)	1 (4)	0 (0)	0 (0)	
Benign-polycystic	1 (1)	0 (0)	1 (4)	0 (0)	0 (0)	
Secondary indication for transplant						
HCC	18 (18)	9 (32)	4 (16)	1 (4)	4 (22)	0.093
Pretransplant hospital stay	18 (18)	6 (21)	4 (16)	6 (21)	2 (11)	0.543
Pretransplant life support	13 (13)	4 (14)	0 (0)	6 (21)	3 (17)	0.222
Listing status						<0.001
Super-urgent	19 (19)	6 (21)	3 (12)	7 (25)	3 (17)	0.759
Priority / Urgent	77 (77)	22 (79)	22 (88)	19 (68)	14 (78)	
Donor						
Age, y	48.5 (38-59)	51 (42-60)	40 (33-55)	47 (32-63)	53 (38-58)	0.640
BMI	25.2 (23-28)	26.7 (24-31)	24.3 (21-26)	26.9 (22-31)	24.8 (23-27)	0.268
Donor type						<0.001
DBD	63 (63)	19 (68)	14 (56)	20 (71)	11 (61)	0.976
DCD	22 (22)	7 (25)	6 (24)	5 (18)	4 (22)	0.995
Split	12 (12)	2 (7)	5 (20)	2 (7)	3 (17)	0.687
Transplant						
CIT, min	479 (405-566)	466 (428-540)	465 (355-540)	510 (404-612)	501 (413-543)	0.786
WIT, min	39 (34-44)	39 (33-42)	39 (33-42)	38 (33-46)	44 (37-49)	0.441
Steatosis (moderate to severe)	12 (12)	7 (25)	0 (0)	3 (11)	2 (11)	0.997
BAR score						
Median	6 (3-8)	6 (4-10)	6 (2-9)	6 (3-9)	6 (3-9)	0.627
>18	8 (8)	4 (14)	0 (0)	2 (7)	2 (11)	
Arterial anatomy						
Normal	60 (61)	17 (61)	14 (56)	17 (61)	12 (67)	0.954
Abberant	39 (39)	11 (39)	11 (44)	11 (39)	6 (33)	
Arterial anastomosis						
1	75 (76)	23 (82)	17 (68)	20 (71)	15 (83)	0.773
>1	19 (19)	4 (14)	6 (26)	7 (25)	2 (11)	0.639
Arterial conduit	3 (3)	0 (0)	2 (8)	0 (0)	1 (6)	0.454
Biliary anastomosis						
Duct-to-duct	72 (72)	25 (89)	16 (64)	17 (61)	14 (78)	0.111
Roux-en-Y	24 (24)	2 (7)	8 (32)	10 (36)	4 (22)	

Data are shown as median (interquartile range) or n (%).

CIT, cold ischemia time; BMI, body mass index; DCD, donation after cardiocirculatory arrest; WIT, warm ischemia time.

TABLE 2.

Recipient, donor, and graft characteristics of liver retransplant

	Entire cohort	Early non-HAT	Early HAT	Late non-HAT	Late HAT	*P*
Number	99 (99)	28 (28)	25 (25)	28 (28)	18 (18)	
Recipient						
Age, y	48.4 (38-57)	54.1 (39-60)	48.6 (45-60)	39.8 (26-48)	51.7 (44-57)	0.012
Sex						
Male	45 (46)	17 (61)	5 (20)	16 (57)	7 (39)	
Female	54 (54)	11 (39)	20 (80)	12 (43)	11 (61)	0.026
MELD	26 (18-33)	34 (27-38)	24 (13-33)	21 (18-28)	13 (9-23)	<0.001
UKELD	59 (54-63)	61 (58-63)	57 (53-62)	61 (55-64)	54 (48-61)	0.039
BMI	25.5 (23-28)	26.1 (24-30)	23.7 (22-27)	25.7 (23-30)	25.9 (22-28)	0.446
Indication for retransplantation (n)						0.020
Primary nonfunction	20 (20)	20 (71)	0 (0)	0 (0)	0 (0)	
Technical (vascular, hepatic infarction, hemorrhage)	46 (47)	1 (4)	25 (100)	2 (7)	18 (100)	
Sepsis (bacterial, fungal)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Rejection	11 (11)	0 (0)	0 (0)	11 (39)	0 (0)	
Recurrence	9 (9)	0 (0)	0 (0)	9 (32)	0 (0)	
De novo malignancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Other hepatic causes	7 (7)	6 (21)	0 (0)	1 (4)	0 (0)	
Other nonhepatic causes	1 (1)	1 (4)	0 (0)	0 (0)	0 (0)	
ITBL	5 (5)	0 (0)	0 (0)	5 (18)	0 (0)	
Pretransplant hospital stay	68 (69)	28 (100)	24 (96)	7 (25)	9 (50)	<0.001
Pretransplant life support	44 (44)	28 (100)	11 (44)	1 (4)	4 (22)	<0.001
Listing status						
Super-urgent	53 (54)	27 (96)	25 (100)	0 (0)	1 (6)	<0.001
Priority / Urgent	45 (46)	1 (4)	0 (0)	27 (96)	17 (94)	<0.001
Donor						
Age, y	50 (36-59)	49.5 (35-63)	51 (30-58)	46 (36-60)	51 (39-57)	0.955
BMI	23.7 (22-27)	25 (22-28)	23.8 (20-27)	22.7 (21-26)	23.8 (22-26)	0.797
Donor type						<0.001
DBD (full-size)	94 (95)	26 (93)	25 (100)	26 (93)	17 (94)	0.763
DBD (split)	5 (5)	2 (7)	0 (0)	2 (7)	1 (6)	0.698
DCD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	n.s.
Transplant						
CIT, min	465 (358-577)	432.5 (308-533)	453 (399-555)	506.5 (378-610)	475 (426-602)	0.272
WIT, min	37 (31-42)	38 (30-40)	39 (34-44)	36.5 (30-48)	32 (27-41)	0.324
Steatosis (moderate to severe)	6(6)	2 (7)	4 (16)	0 (0)	0 (0)	0.494
BAR score						
Median	15 (10-20)	21 (18-24)	13 (9-20)	11 (10-16)	8 (6-16)	<0.001
>18	37 (37)	23 (82)	8 (32)	3 (11)	3 (17)	0.302
Arterial anatomy						
Normal	65 (66)	18 (64)	15 (60)	20 (71)	12 (67)	0.939
Abberant	34 (34)	11 (36)	11 (40)	10 (29)	6 (33)	
Arterial anastomosis						
1	42 (42)	18 (64)	9 (36)	14 (50)	1 (6)	<0.001
>1	12 (12)	7 (25)	2 (8)	1 (4)	2 (11)	0.160
Arterial conduit	45 (46)	3 (11)	14 (56)	13 (46)	15 (83)	<0.001
Biliary anastomosis						
Duct-to-duct	53 (54)	25 (89)	14 (56)	10 (36)	4 (22)	0.003
Roux-en-Y	44 (44)	3 (11)	11 (44)	17 (61)	13 (72)	

Data are shown as median (interquartile range) or n (%).

n.s., nonsignificant (statistical analysis with Chi-square test impossible); ITBL, ischemic type biliary lesion.

Quest for Ideal Graft Choice and Lack of Predictive Tools to Prognosticate Inferior Survival in L-HAT

Akin to all other groups, only grafts from standard donors after brain death (DBD) were used for re-LT in L-HAT patients (Table 2). Avoidance of marginal grafts from overweight or old donors demonstrates the selection process for the best organs as required in sick retransplant candidates. The higher acceptance rate of steatotic organs in early re-LT was most likely driven by the urgency of organ replacement and lack of alternative organ offers. Recipient/donor matching in early re-LT carried the highest risk for transplantation as suggested by a BAR score of 19 (14-22) compared with a

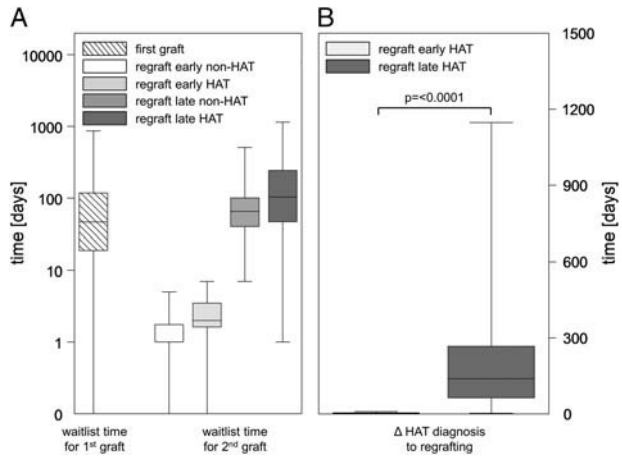

FIGURE 1. Access to second grafts was restricted for L-HAT patients. A, L-HAT was associated with the longest transplant waitlist time compared with late non-HAT re-LT candidates or waitlist time for the first liver graft. B, Late HAT patients experienced a significant time lag between diagnose, listing, and transplantation in sharp contrast to early HAT retransplant candidates with premium graft access by super-urgent listing status. Data are shown as n (%).

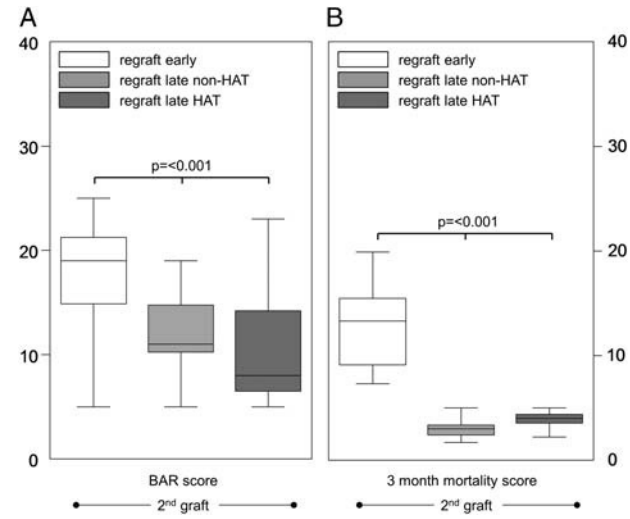

FIGURE 3. Disease severity of L-HAT patients is not reflected in the current allocation system. A, Similar to MELD and UKELD, BAR risk score did not give evidence of the advanced liver disease of L-HAT patients. B, The 3-month mortality score falsely predicted better survival in late re-LT subgroups. Data are shown as median (interquartile range).

low BAR score of 11 (10-16) and 8 (6-16) in the late non-HAT group and L-HAT recipients, respectively (Figure 3A). Correspondingly, the 3-month mortality score predicted significantly better patient survival in the late re-LT subgroups (Figure 3B).

Ninety-day mortality, 1-year patient survival, and 1-year graft survival of the entire re-LT cohort reached 12%, 86%, and 82%, respectively. In sharp contrast to the prognostication of the utility-based prediction scores, early mortality within 90 days was significantly higher (n = 5; 28%) in the L-HAT group heavily impacting on considerably inferior long-term patient and graft survival (1 year, 65% each) compared with all other groups (Figures 4A-C). All regrafted L-HAT patients with 90-day mortality died on the critical care unit during their index admission compared with 11%, 16%, and 0% of early non-HAT, E-HAT, and late non-HAT re-LT recipients, respectively. The early death of L-HAT patients was driven by sepsis and multiorgan failure (MOF) (Figure 4D). Notably, L-HAT patients with early mortality after re-LT were observed to have a markedly higher rate of multidrug-resistant infections before regrafting compared with L-HAT re-LT survivors beyond 90 days (83% vs 46%, $P = 0.596$).

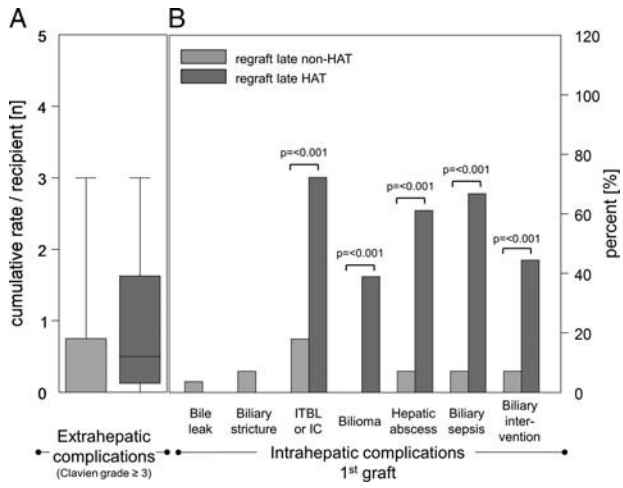

FIGURE 2. L-HAT causes a distinctive plethora of intrahepatic complications of the failing first liver graft. A and B, Systemic complications in Clavien category 3 or above after the first liver graft were comparable in between late subgroups, whereas L-HAT specific IC caused a high rate of transplant interval intrahepatic complications necessitating biliary interventions in the L-HAT subpopulation during the waiting time for re-LT. Data are shown as median (interquartile range) or n (%).

Optimal Retransplant Interval Improves Results in L-HAT

Comparing the trends in short- and long-term survivals during waitlist time, we observed an optimized window of opportunity for re-LT in L-HAT (Figure 4E). The best 1-year patient survival with 77% could be reached by a limited median waiting time of 42 (10-16) days for a regraft and, similarly, overall greatest patient survival (64%) at the median follow-up of 955 (541-1662) days was achieved in L-HAT patients that were retransplanted after a median waiting time of 45 (10-146) days. An analogous re-LT timepoint of 47 (11-198) days likewise yielded the lowest 90-day mortality of 13% in L-HAT, and this was comparable to results in early re-LT. Outcomes of re-LT for L-HAT outside this interval were inferior.

DISCUSSION

Re-LT demand has declined from historical 19% in the pre-MELD era to 8% in the post-MELD era.[7] We observed an analogous decrease in the rate of re-LT at our institution from former 8% in the pre-MELD era to currently 5.7% most likely based on improved immunosuppression and long-term graft survival.[8] It appears however that technical complications, such as HAT, remain a major indication for re-LT, which is corroborated in both our institutional data and data from other large centers.[8,9] Previous history of HAT, low donor body weight, and complex arterial reconstruction have been described as risk factors for the development of

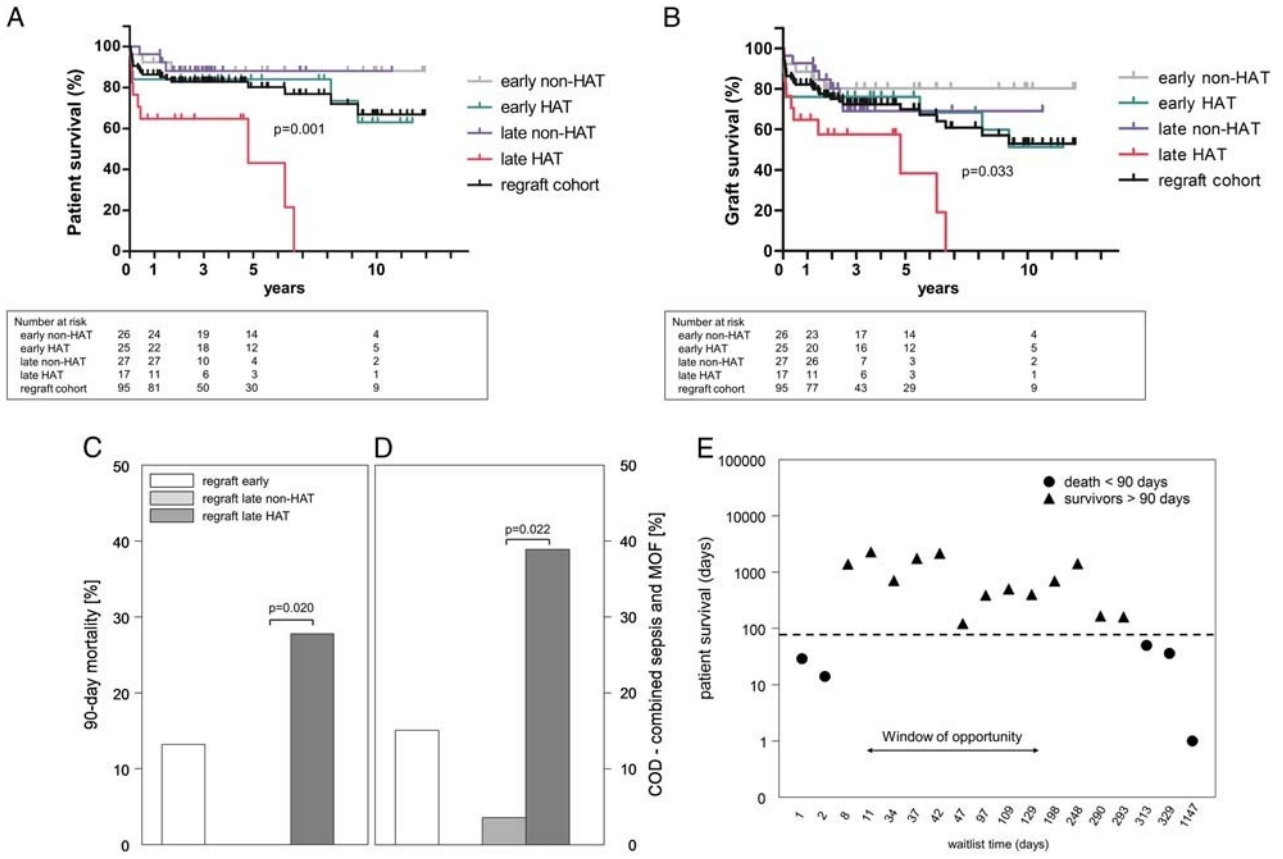

FIGURE 4. Re-LT for L-HAT is associated with a significantly higher early mortality driven by sepsis and MOF and optimized timing of re-LT yields superior results in L-HAT. A-D, Re-LT for indications other than HAT achieved comparable short- and long-term patient and graft survival but there is significantly higher early mortality in the L-HAT subgroup driven by sepsis and MOF. E, Access to a second liver graft after a median waitlist time of 6 weeks achieved the best short- and long-term outcome in re-LT for L-HAT.

HAT.[4,10-12] In an attempt to prevent HAT, all current adult LT recipients are placed on long-term antiplatelet therapy with low-dose aspirin which may have contributed to lower the incidence of HAT from 7.6% to 6.5% at our institution.[4]

Herein, we focused on outcome after re-LT in L-HAT, and we demonstrate that results are significantly worse in this patient group compared with all other indications for re-LT. Yet, re-LT in L-HAT is feasible as the actual 1-year patient survival after re-LT in L-HAT with 65 % surpassed the estimated waitlist survival of 53 % of listed candidates for the same indication.[13] Additionally, the posttransplant survival outcome in L-HAT remains somewhat stable after 1 year. It therefore complies with the 50% of 5-year survival expectancy rule imposed by UK organ allocation policy and is comparable to results of high-risk groups as classified by United Network of Organ Sharing Rosen risk score.[2]

Different prognostic models have been designed to capture predictors of survival in simple scores with the aim to aid in donor-recipient matching. Re-LT is included as a risk factor in utility-based models, such as BAR score, survival outcome following liver transplantation (SOFT) score, and 3-month mortality score, which have all been validated based on pretransplant parameters.[3,14] Disappointingly, both BAR score and 3-month mortality score failed to forecast the inferior survival in the L-HAT group in our study, and indeed, scores predicted the opposite of the observed outcome. This observation is in accordance with the results of a recent stratified analysis for low and high MELD posttransplant outcome which demonstrated low positive predictive values in posttransplant mortality for various risk classification models, including D-MELD, delta-MELD, donor risk index, University of California Los-Angeles - futility risk score, SOFT score, and BAR score.[15] Taken together, we conclude that both tested utility-based prediction scores are futile for prognostication of re-LT outcome in L-HAT.

The most reasonable explanation for the lack of accurate predictive tools for re-LT outcome in L-HAT is that the tested models are heavily dominated either by acuity of liver disease or MELD. The MELD score predicts waitlist mortality in both primary transplant and re-LT candidates but poorly defines outcome after LT due to the absence of donor factors.[16,17] Additionally, disease burden of L-HAT with the full spectrum of biliary complications in the first graft and concomitant biliary sepsis is not reflected by MELD as clearly demonstrated in our re-LT cohort. The low MELD score of L-HAT patients would imply clinical stability but MELD score was not predictive of waitlist mortality in L-HAT which reportedly cumulates to 18%.[18]

We confirm that sepsis and MOF drive early mortality in re-LT for L-HAT.[11] This is not surprising giving the high rate of pretransplant multidrug-resistant bacterial and fungal infections in L-HAT retransplant candidates accumulating to 61% during waitlist time which were associated with early death after re-LT in L-HAT. Concordantly, intercurrent multidrug-resistant bacteremia places L-HAT re-LT candidates at risk for both death on the waiting list and post-retransplant death.[18,19] Furthermore, pretransplant sepsis

was recently identified as independent predictor of futile outcome in high-acuity patients.[20]

L-HAT retransplant candidates seem to be less disadvantaged when rated by UKELD, which forms the basis for prioritization in the urgency-based organ allocation in the UK and United States (MELD-Na for MELD > 11).[17,21] Yet, relisted L-HAT patients waited longest for acceptable organ offers and accumulated the most hospital readmission days during the waitlist time which forms a major healthcare burden. Conservative management of L-HAT is only successful in a minority, and many L-HAT patients are either too sick to be relisted or die on the waiting list.[12,18] In fact, although it is reported that the incidence of L-HAT exceeds the occurrence of early HAT, re-LT for L-HAT is less common.[4]

Two essential details seem to play a fundamental role in the time lag to re-LT in L-HAT. First, to compensate for the compromised medical status of the re-LT candidate, selection of nonmarginal DBD grafts is mandatory to maximize the individual transplant benefit.[22] Second, L-HAT patients are in fierce competition not only with all other retransplant candidates but especially with super-urgent de novo liver transplant candidates in their demand for the optimal graft from the limited donor pool. L-HAT patients are however bypassed in the current organ distribution system because their biliary disease is poorly reflected within urgency-based organ allocation models but exemption status is not granted either.

Emergency status has been introduced as a tool to pay justice to the sickest-first concept while both standard and nonstandard exception status should counterbalance unfairness in graft access.[17] Pertinent examples are standard exception for cholangiopathies, such as primary sclerosing cholangitis within Eurotransplant allocation zone, the worldwide eligibility for emergency status in E-HAT, and last but not least, the possibility to apply for nonstandard exception in failed transplantation of donor after cardiocirculatory death grafts in the United States.[23] Analogous to the two latter, there are no alternative nontransplant strategies to rescue L-HAT patients with insufficient arterial collateralization and failed conservative management. The human right on equality, justice, equity, and access to quality healthcare is laid down in the "Universal Declaration of Bioethics and Human Rights" of the United Nations Educational, Scientific and Cultural Organization which is a legally binding ethical framework for organ allocation policies.[24] The medical and moral responsibility for recipients of failing transplant organs therefore dictates the principle that efforts must be made for the individual transplant benefit of the eligible retransplant candidate with retained reasonable physiologic reserve. Hence, relisted L-HAT patients should be granted timely graft access.

However, it is of paramount importance to note that re-LT during a certain period yields more favorable results in L-HAT than disadvantageous immediate or very late re-LT. This is best explained by 2 facts. First, the deep-tissue source of infection is usually uncontrolled at diagnosis of L-HAT, which can result in early posttransplant sepsis. Optimal medical treatment of the bacterial inflammation before re-LT could allow for either disease stabilization or might unmask patients unfit for re-LT that would most likely be nonsurvivors. Second, as stated above, a long waiting time for re-LT is associated with intercurrent multiresistant infections and posttransplant death.

The main limitation of our retrospective analysis is the small number of patients included from a single institution during a decade impacting on the statistical significance of our findings. Our approach however harbours the strengths of consistent prospective data collection, low bias by the surgeon's expertise at a high-volume center and accurate reflection of contemporary results in the complex field of liver retransplantation.

In summary, L-HAT retransplant candidates have the longest waiting time until re-LT and inferior transplant outcome. Contributing factors to underprivileged graft access are the competition for the ideal organ, the inability to accurately measure disease burden of liver graft failure in L-HAT based on a lack of acceptable tools and the absence of rescue strategies in the current allocation models for L-HAT–associated graft failure. Importantly, we identify an optimal time interval for re-LT in L-HAT with the view to improve outcomes. Currently, it remains a matter of debate how timely and fair graft access can be granted for L-HAT retransplant candidates. In theory, this could be facilitated by internal prioritization in center-based allocation models or timed exemption status in national allocation models if L-HAT retransplant candidates with retained physiological reserve and controlled infection remain longer than 6 weeks on the waitlist.

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