Hospitalization Before Liver Transplantation Predicts Posttransplant Patient Survival: A Propensity Score–Matched Analysis

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In contrast to donor factors predicting outcomes of liver transplantation (LT), few suitable recipient parameters have been identified. To this end, we performed an in-depth analysis of hospitalization status and duration prior to LT as a potential risk factor for posttransplant outcome. The pretransplant hospitalization status of all patients undergoing LT between 2005 and 2016 at the Charité-Universitätsmedizin Berlin was analyzed retrospectively using propensity score matching. At the time of organ acceptance, 226 of 1134 (19.9%) recipients were hospitalized in an intensive care unit (ICU), 146 (12.9%) in a regular ward (RW) and 762 patients (67.2%) were at home. Hospitalized patients (RW and ICU) compared with patients from home showed a dramatically shorter 3-month survival (78.7% versus 94.4%), 1-year survival (66.3% versus 87.3%), and 3-year survival (61.7% versus 81.7%; all $P < 0.001$), whereas no significant difference was detected for 3-year survival between ICU and RW patients (61.5% versus 62.3%; $P = 0.60$). These results remained significant after propensity score matching. Furthermore, in ICU patients, but not in RW patients, survival correlated with days spent in the ICU before LT (1-year survival: 1-6 versus 7-14 days: 73.7% versus 60.5%, $P = 0.04$; 7-14 days versus >14 days, 60.5% versus 51.0%, $P = 0.006$). In conclusion, hospitalization status before transplantation is a valuable predictor of patient survival following LT.

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Choosing the right organ for the right recipient is crucial in liver transplantation (LT).[1] In many countries, liver allocation is based on the Model for End-Stage Liver Disease (MELD) score and defined exceptions.[2,3] However, when an organ is being offered, the decision whether to accept an organ remains with the treating physicians. A lot of helpful data have been generated for donors and for perioperative parameters, and they have been included in various risk scores.[4-6] On the recipient side, data are scarce. MELD, which is not only a predictor of liver disease mortality, has been shown to have a significant influence on posttransplant survival.[7] However, MELD or the modified MELD-sodium scores are solely based on 3 and 4 laboratory values, respectively, and may not properly reflect the risk of fatal outcomes after LT.[8] Although experienced physicians can gauge their patients' health status relatively accurately, a more objective assessment using available predictive parameters of transplant outcomes should support decision making and eventual organ allocation.[9,10] Thus, other objective parameters that

Abbreviations: BAR, balance of risk; BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; CT, computed tomography; DRI, donor risk index; FFP, fresh frozen plasma; HR, hazard ratio; HU, high-urgency; ICH, intracerebral hemorrhage; ICU, intensive care unit; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NS, not significant; RW, regular ward; SD, standard deviation; SOFT, survival outcomes following liver transplantation; UNOS, United Network for Organ Sharing.

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predict outcomes after LT are urgently needed and may be included in risk scores and would be a helpful tool for decision making.

Existing outcome scores, including the balance of risk (BAR) score,(11) D-MELD,(6) or survival outcomes following liver transplantation (SOFT) score,(7) offer a more objective assessment, but they have their own specific disadvantages. Some are complex with over 15 parameters. Some still include subjective clinical assessments of ascites and encephalopathy, and they do not take into consideration the patient's general health status. Recently, several objective surrogate parameters for the general status of the patients, which correlate well with posttransplant patient survival, have been studied, such as malnutrition (Royal Free Hospital Global Assessment tool), low muscle mass (psoas area on computed tomography [CT] scan), and frailty tests.(12-15) Unfortunately, the health status of LT candidates can deteriorate rapidly, and constantly updating these sophisticated scores is impractical.

Hospitalization status at the time of LT represents another surrogate parameter for the general health status of a listed patient that is easily available at any time point. It subsumes comorbidities, fitness, and biological age among other things and has been described as an adverse predictor for various outcome points after LT, such as morbidity, survival, and length of stay after LT as well as posttransplant hospital readmissions.(16-19) These findings were mostly limited to the time point directly prior to LT and did not evaluate in detail the period of time these patients had been hospitalized.

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The relationship not only between patient survival after LT and hospitalization status but also hospitalization duration has not yet been fully explored in LT recipients. We hypothesized that hospitalization time before LT would be an easily available and relevant predictor for posttransplant patient survival after LT.

Patients and Methods

SETTING AND PATIENTS

A retrospective single-center study from the Charité University Hospital, Berlin, Germany was performed. All consecutive adult LTs and combined liver-kidney transplantations between January 2005 and December 2016 were analyzed. Deceased (full size and split) as well as living donor grafts were included. No circulatory death donors were used because this type of donation is not permitted in Germany.

DATA COLLECTION

Data were collected from electronic health records. Because of data protection, only data from our own institution were available for evaluation of hospital admission. Admissions to other hospitals can therefore not be precluded, although patients are urged to report every hospital stay.

STUDY VARIABLES

The primary endpoints were defined as patient survival at 3 months, 1 year, and 3 years after LT. Secondary endpoints included intensive care unit (ICU) stay after LT and total length of hospital stay after LT.

Hospitalization status at the time of LT and the duration of hospitalization prior to LT were assessed. Observation time was limited to 30 days prior to LT. This time span was selected on the basis of recertification schedules in the LT programs by United Network for Organ Sharing (UNOS) and Eurotransplant to reflect short-term changes in patients on the liver waiting list. Hospitalization status at the time of listing may coincide for some patients but was not primarily investigated in this study.

Hospitalization was further categorized into regular ward (RW) and ICU stays. Patients were assigned to these groups by the ward in which they were treated directly prior to LT. Subgroups were analyzed by hospitalization status at the time of LT: days hospitalized in the ICU directly before LT for patients in the ICU, total hospital days before LT for patients in a RW, and number of prior hospital admissions during the last 30 days for patients from home.

In the German LT program, patients can receive a high-urgency (HU) status and are then prioritized in the allocation process if they suffer from fulminant acute liver failure or acute graft failure <15 days after transplant (comparable to Organ Procurement and Transplantation Network status 1A). Dialysis prior to LT was defined according to the Eurotransplant Liver Allocation System.

STATISTICAL ANALYSES

Patient characteristics were examined with descriptive statistics (using frequencies and percentages), the Pearson chi-square test for categorical data (using mean and standard deviation [SD]), independent 2-sample *t* test for parametric continuous data (using median and interquartile range [IQR]), and Mann-Whitney U test for nonparametric continuous data.

Hospitalization days were stratified into 4 groups for the survival analysis: 0, 1-6, 7-14, and >14 days. Cumulative overall survival was calculated using a Kaplan-Meier analysis, and groups were compared with the log-rank test. To compare the effect of hospitalization status and time without the influence of known risk factors for survival after LT, we used propensity score matching. Patient groups were matched by recipient age, recipient body mass index (BMI), recipient sex, laboratory MELD score, indication for LT, MELD exceptional status, HU status, retransplantation, split organ, cold ischemia time (CIT), donor age, donor BMI, and donor sex. The propensity score was calculated using multiple logistic regression analysis, and the matching was executed using the nearest neighbor method. As recommended in the work by Austin, a caliper width of 0.2 of the standard deviation of the logit of the propensity score was chosen.[20] After the matching procedure, the comparability of matched groups was analyzed by the equalized balance of covariates.

To evaluate predictors for 1-year patient survival after LT and the ability of hospitalization time before LT as a predictor for posttransplant survival, Cox regression was used. Variables found to be significant in the univariate analysis were then candidates for the multivariate analysis using both forward and backward procedures with a significance level for *P* of 0.05 for model entry and 0.10 for removal. Missing data were below 5% for all variables considered for the multivariate regression, and therefore, no procedures to impute missing data were used. Statistical analyses were carried out using SPSS Statistics, version 25 (IBM Corporation, Armonk, NY). For propensity score matching, R, version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria); SPSS Statistics Essentials plug-in, version 25 (IBM Corp., Armonk, NY); and SPSS plug-in PS Matching in SPSS, version 3.04 (IBM Corp.) were additionally used.[21] A P value of <0.05 was considered significant. The study was approved by the local ethics commission (EA1/369/16).

Results

A total of 1134 LTs were performed during the study period. This included 1073 (94.6%) full-size grafts and 61 (5.4%) split grafts. A vast majority were solitary LTs, and only 25 (2.2%) were combined liver-kidney transplantations. A total of 157 (13.8%) patients received retransplantations (84.1% first retransplantations). Patients had HU status in 133 (11.7%) cases. Baseline patient and clinical characteristics are presented in Table 1.

Approximately two-thirds (n = 762; 67.2%) of the recipients were at home prior to LT, whereas 146 (12.9%) were hospitalized in a RW, and 226 (19.9%) were treated in an ICU directly prior to LT. Patients in a RW prior to LT had a median hospital stay of 14.5 (IQR, 4.8-28.5) days before LT. Patients hospitalized in the ICU before LT had a median total hospital stay of 11.0 (IQR, 5.0-22.5) days and a median ICU stay of 6.0 (IQR, 3.0-13.0) days before LT. Patient characteristics by hospitalization status are presented in Table 2.

ICU patients were significantly younger than patients coming from home (mean age 49.3 versus 54.3 years; $P < 0.001$), but they were sicker according to their higher laboratory MELD at day of LT (median laboratory MELD, 35 versus 14; $P < 0.001$). Similarly, patients in an ICU compared with patients from RW were more critically ill (median laboratory MELD, 35 versus 27; $P < 0.001$) and younger (mean age, 49.3 years versus 52.3 years; $P = 0.02$). Median (IQR) waiting time was significantly shorter for patients who were hospitalized directly before LT: ICU versus RW, 3.0 (1.0-13.2) days versus 63.5 (13.0-258.2) days ($P < 0.001$); RW versus home,

TABLE 1. Demographic, Clinical, and Donor Characteristics of All Consecutive LTs From 2005 to 2016

Characteristic	Study Population (n = 1134)
Age at LT, years	53.1 ± 10.7
Sex, male	726 (64.0)
BMI, kg/m^2	26.4 ± 4.9
Indication	
Cirrhosis	430 (37.9)
Virus-related	100 (8.8)
Alcoholic	245 (21.6)
Combined viral and alcoholic	10 (0.9)
Other	75 (6.6)
Liver tumors	318 (28.0)
Retransplantation	157 (13.8)
Cholestatic disease	93 (8.2)
Acute liver failure	50 (4.4)
Other	86 (7.6)
Listing details	
Waiting time, days	99.0 (14.0-313.8)
Laboratory MELD, score	17 (11-27)
Match MELD, score	22 (15-29)
HU status	133 (11.7)
Retransplantation	157 (13.8)
Graft and surgical parameters	
CIT, minutes	561.0 ± 185.9
Length of transplantation, minutes	336.1 ± 90.5
Erythrocyte concentrates	6.0 (3.0-10.0)
FFP	19.0 (13.0-28.0)
Hospitalization status at transplant	
Home	762 (67.2)
RW	146 (12.9)
ICU	226 (19.9)
Posttransplant ICU stay, days	9.0 (6.0-20.0)
Posttransplant hospital stay, days	31.0 (22.0-54.0)
Donor characteristics	
Age, years	52.9 ± 17.1
Sex, male	569 (50.2)
BMI, kg/m^2	25.9 ± 4.5
ICU stay, days	3.0 (2.0-7.0)

NOTE: Data are given as mean ± SD, median (IQR), or n (%).

63.5 (13.0-258.2) days versus 153.5 (49.0-406.8) days ($P < 0.001$).

Patients transplanted from the ICU compared with patients transplanted from home showed a significantly lower 3-month (75.7% versus 94.4%), 1-year (63.7% versus 87.3%), and 3-year (61.5% versus 81.6%) survival ($P < 0.001$ for all; Fig. 1A). No significant differences between patients from ICU and patients from a RW were seen for 3-month survival (75.7% versus 83.6%; $P = 0.08$), 1-year survival (63.7% versus 70.5; $P = 0.10$), and 3-year survival (61.5% versus 62.3%; $P = 0.60$). After propensity score matching for known outcome risk factors, 3-year patient survival of the hospitalized groups remained significantly worse compared with nonhospitalized patients: ICU versus home, 59.5% versus 81.0% ($P = 0.04$); and RW versus home, 59.5% versus 81.0% ($P = 0.04$). Again, there was no significant survival benefit of RW compared with ICU patients (ICU versus RW, 59.5% versus 59.5%; $P > 0.99$; Fig. 1B). For the characteristics of the subgroups by hospitalization status after Propensity Score Matching, see Supporting Table 1. The overall 3-year survival of the study group was 75.1%.

A subgroup analysis revealed that the survival of patients from home was not affected by the number of recent hospital admissions in the 30 days prior to LT (3-year patient survival: 0 versus 1 admission, 82.2% versus 81.3%, $P = 0.74$; 0 versus ≥2 admissions, 82.2% versus 76.9%, $P = 0.37$; 1 versus 2 admissions, 81.3% versus 76.9%, $P = 0.50$; Fig. 2A). For the characteristics of subgroups by recents hospital admissions, see Table 3 and Supporting Table 2. Likewise, after propensity score matching, no differences were found between patients with and without recent hospital admissions ($P = 0.37$; Fig. 2B). For the characteristics of the subgroups by recents hospital admissions after Propensity Score Matching, see Supporting Table 3.

In patients hospitalized in a RW prior to LT, in-depth analysis demonstrated that posttransplant survival in this group did not correlate with the duration of pretransplant hospital stay (3-year patient survival: 1-6 days versus 7-14 days versus >14 days, 59.1% versus 74.4% versus 60.3%; overall $P = 0.54$; Fig. 3A). For the characteristics of the subgroups classified by length of hospital stay, see Table 4 and Supporting Table 4. In the survival analysis of matched groups, we found similar results ($P = 0.41$; Fig. 3B). For the characteristics of the subgroups classified by length of hospital stay after Propensity Score Matching, see Supporting Table 5.

Patients who received ICU treatment but were transferred back to the RW due to recovery showed comparable survival to patients from the RW who had never been in the ICU (3-year patient survival for patients in the RW at the time of organ allocation but with recent ICU stay versus patients without a recent ICU stay: 66.7% versus 60.4%; $P = 0.48$).

TABLE 2. Patient Characteristics by Hospitalization Status

	Home (n = 762; 67.2%)	RW (n = 146; 12.9%)	ICU (n = 226; 19.9%)	*P* Value (All Groups)
Age at LT, years	54.3 ± 10.0	52.3 ± 10.4	49.3 ± 12.2	<0.001
Sex, male	517 (67.8)	85 (58.2)	124 (54.9)	<0.001
BMI, kg/m^2	26.7 ± 4.8	26.2 ± 5.2	25.5 ± 5.0	0.008
Laboratory MELD, score	14 (10-19)	27 (19-33)	35 (26-40)	<0.001
Retransplantation	23 (3.0)	24 (16.4)	110 (48.7)	<0.001
HU status	0	5 (3.4)	128 (56.6)	<0.001
Liver-kidney transplantation	22 (2.9)	2 (1.4)	1 (0.4)	0.07
Waiting time, days	153.5 (49.0-406.8)	63.5 (13.0-258.2)	3.0 (1.0-13.2)	<0.001
Time in hospital before LT, days	0	14.5 (4.8-28.5)	11.0 (5.0-22.2)	—
In ICU before LT, days	0	0	6.0 (3.0-13.0)	—
CIT, minutes	567.1 ± 193.8	577.6 ± 208.1	529.5 ± 133.4	0.56
Length of LT, minutes	336.6 ± 81.2	369.2 ± 108.6	313.3 ± 100.7	<0.001
Erythrocyte concentrates	5.0 (2.0-8.0)	9.0 (6.0-13.0)	7.0 (4.0-13.0)	<0.001
FFP	18.0 (12.0-27.0)	24.0 (18.0-31.0)	20.0 (14.0-31.0)	<0.001
Posttransplant ICU stay, days	8.0 (5.0-13.0)	10.0 (6.0-27.0)	22.0 (10.8-54.5)	<0.001
Posttransplant hospital stay, days	28.0 (22.0-44.0)	37.5 (25.8-61.8)	47.0 (27.0-77.2)	<0.001

NOTE: Data are given as mean ± SD, median (IQR), or n (%).

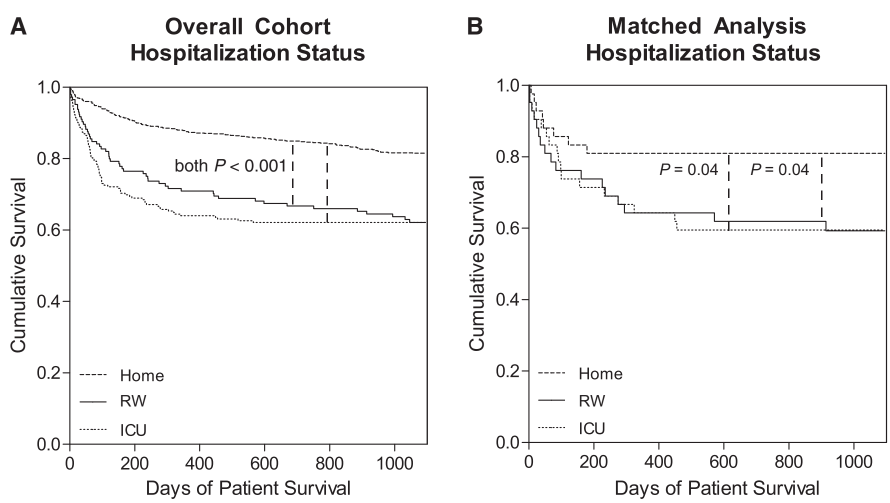

FIG. 1. Kaplan-Meier survival analysis by hospitalization status prior to transplantation. (A) Unmatched analysis (overall cohort) and (B) after the propensity score–matched analysis (matched cohort). The matching covariates are recipient age, recipient BMI, recipient sex, laboratory MELD score, indication for LT, MELD exceptional status, HU status, retransplantation, split organ, CIT, donor age, donor BMI, and donor sex. Patients in the unmatched analysis: home (n = 762), RW (n = 146), and ICU (n = 226). Trends for the unmatched analysis: overall trend, $P < 0.001$; home versus RW, $P < 0.001$; home versus ICU, $P < 0.001$; RW versus ICU, $P = 0.60$. Patients in the matched analysis for all groups, n = 42. Overall trend, $P = 0.08$; home versus RW, $P = 0.04$; home versus ICU, $P = 0.04$; RW versus ICU, $P > 0.99$.

When investigating patients from the ICU who received LT, posttransplant 3-year survival decreased with increasing duration of ICU stay before LT: 1-6 versus 7-14 versus >14 days, 71.0% versus 53.3% versus 45.2%; 1-6 versus 7-14 days, $P = 0.01$; 1-6 versus >14 days, $P = 0.004$; Fig. 4A. For the characteristics of the classified by length of ICU stay, see Table 5 and Supporting Table 6. These results were consistent in the propensity score–matched analysis for 3-year patient survival between the matched groups:

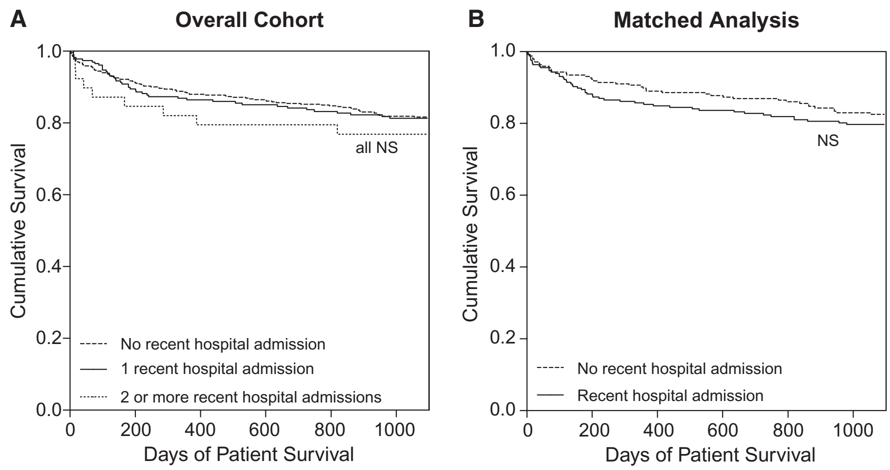

FIG. 2. Kaplan-Meier survival analysis for patients at home prior to transplantation by number of previous hospital admissions in the last month before transplantation. (A) Unmatched analysis (overall cohort) and (B) after the propensity score–matched analysis (matched cohort). The matching covariates are recipient age, recipient BMI, recipient sex, laboratory MELD score, indication for LT, MELD exceptional status, HU status, retransplantation, split organ, CIT, donor age, donor BMI, and donor sex. Patients in the unmatched analysis: no recent hospital admissions (group 1, n = 484), 1 recent hospital admission (group 2, n = 230), and 2 or more recent hospital admissions (group 3, n = 39). Trends for the unmatched analysis: overall trend, $P = 0.66$; group 1 versus group 2, $P = 0.73$; group 1 versus group 3, $P = 0.37$; and group 2 versus group 3, $P = 0.50$. Patients in the matched analysis: both groups, n = 246, $P = 0.37$.

TABLE 3. Characteristics for Patients at Home Before LT Classified by Recent Hospital Stay

	Recent Hospital Stay (n = 269)	Without Recent Hospital Stay (n = 485)	*P* Value
Age at LT, years	55.1 ± 10.1	53.9 ± 9.8	0.11
Sex, male	195 (72.5)	316 (65.2)	**0.04**
BMI, kg/m^2	26.8 ± 5.0	26.7 ± 4.8	0.81
Laboratory MELD	16 (10-20)	13 (9-18)	<**0.001**
Match MELD	20 (14-25)	18 (13-25)	0.41
Exceptional MELD	67 (24.9)	141 (29.1)	0.21
Retransplantation	14 (5.2)	9 (1.9)	**0.01**
HU status	0	0	—
Dialysis	9 (3.3)	22 (4.5)	0.43
Waiting time, days	58.0 (15.5-200.0)	209.0 (92.0-482.5)	<**0.001**
Posttransplant ICU stay, days	8.0 (5.0-13.0)	8.0 (5.0-13.0)	0.77
Posttransplant hospital stay, days	29.0 (21.0-45.0)	28.0 (22.0-44.0)	0.97

NOTE: Data are given as mean ± SD, median (IQR), or n (%). Information about recent hospital stay missing for 9 patients. Bold indicates significance at $P < 0.05$. The data presented here correspond to Fig. 2A.

1-6 versus 7-14 days, $P = 0.07$; 1-6 versus >14 days, $P = 0.03$ (Fig. 4B). For the characteristics of the classified by length of ICU stay after Propensity Score Matching, see Supporting Table 7.

Both survival and posttransplant median health care utilization varied according to hospitalization status before LT. Patients transplanted from home spent a median (IQR) of 8.0 days (5.0-13.0 days) in the ICU after LT compared with 10.0 days (6.0-27.0 days) spent by patients transplanted from a RW and 22.0 days (10.8-54.5 days) by patients who were already in the ICU prior to LT (home versus RW and RW versus ICU, both $P < 0.001$; Table 2). Similar results were found for median (IQR) total length of stay after LT: home, 28.0 days (22.0-44.0 days); RW, 37.5 days (25.8-61.8 days); and ICU, 47.0 days

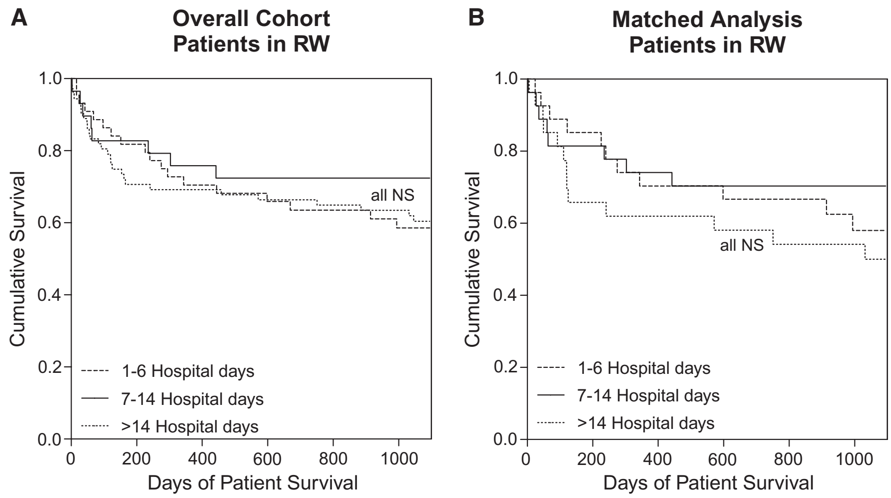

FIG. 3. Kaplan-Meier survival analysis for patients hospitalized in a RW prior to transplantation by number of total hospital days directly before transplantation. (A) Unmatched analysis (overall cohort) and (B) after propensity score–matched analysis (matched cohort). The matching covariates are recipient age, recipient BMI, recipient sex, laboratory MELD score, indication for LT, MELD exceptional status, HU status, retransplantation, split organ, CIT, donor age, donor BMI, and donor sex. Patients in the unmatched analysis: 1-6 hospital days (group 1, n = 44), 7-14 hospital days (group 2, n = 29), and >14 hospital days (group 3, n = 73). Trends for the unmatched analysis: overall trend, $P = 0.54$; group 1 versus group 2, $P = 0.34$; group 1 versus group 3, $P = 0.91$; and group 2 versus group 3, $P = 0.29$. Patients in the matched analysis: all groups, n = 27. Trends for the matched analysis: overall trend, $P = 0.41$; group 1 versus group 2, $P = 0.52$; group 1 versus group 3, $P = 0.45$; and group 2 versus group 3, $P = 0.20$.

TABLE 4. Characteristics for Patients in a RW Before LT Classified by Length of Hospital Stay

				P Value			
	1-6 Hospital Days (n = 44)	7-14 Hospital Days (n = 29)	>14 Hospital Days (n = 72)	All Groups	1-6 Days Versus 7-14 Days	1-6 Days Versus >14 Days	7-14 Days Versus >14 Days
Age at LT, years	53.1 ± 8.3	50.8 ± 9.7	52.3 ± 11.8	0.65	0.28	0.71	0.53
Sex, male	28 (63.6)	18 (62.1)	39 (54.2)	0.50	0.89	0.28	0.43
BMI, kg/m^2	26.7 ± 5.4	26.0 ± 7.2	26.0 ± 4.0	0.80	0.67	0.47	0.99
Laboratory MELD	23 (17-32)	23 (17-32)	29 (20.5-34.5)	0.07	0.75	**0.03**	0.13
Match MELD	24 (18-32)	26.5 (18.25-33.75)	29 (23.5-35)	0.06	0.86	**0.03**	0.10
Exceptional MELD	6 (13.6)	3 (10.3)	11 (15.3)	0.82	0.68	0.83	0.53
Retransplantation	6 (13.6)	2 (6.9)	16 (22.2)	0.15	0.37	0.27	0.07
HU status	0	2 (6.9)	2 (2.8)	0.26	0.08	0.17	0.56
Dialysis	0	5 (17.2)	25 (34.7)	**<0.001**	**0.004**	**<0.001**	0.09
Waiting time, days	132.0 (47.8-417.2)	40.0 (6.0-152.0)	41.5 (8.8-233.8)	**0.01**	**0.008**	**0.009**	0.66
Posttransplant ICU stay, days	14.5 (7.2-41.8)	8.0 (6.0-12.5)	10.5 (6.0-24.0)	**0.04**	**0.009**	0.07	0.31
Posttransplant hospital stay, days	41.5 (25.2-71.5)	29.0 (21.0-42.5)	42.5 (29.0-64.75)	**0.02**	**0.03**	0.85	**0.006**

NOTE: Data are given as mean ± SD, median (IQR), or n (%). Bold indicates significance at $P < 0.05$. The data presented here correspond to Fig. 3A.

(27.0-77.2 days); home versus RW, $P < 0.001$; RW versus ICU, $P = 0.06$. Furthermore, in-hospital mortality after LT was higher in patients hospitalized prior to LT: home, 7.2%; RW, 21.4%; ICU, 29.4%; RW versus home and ICU versus home, both $P < 0.001$. No significant differences were found

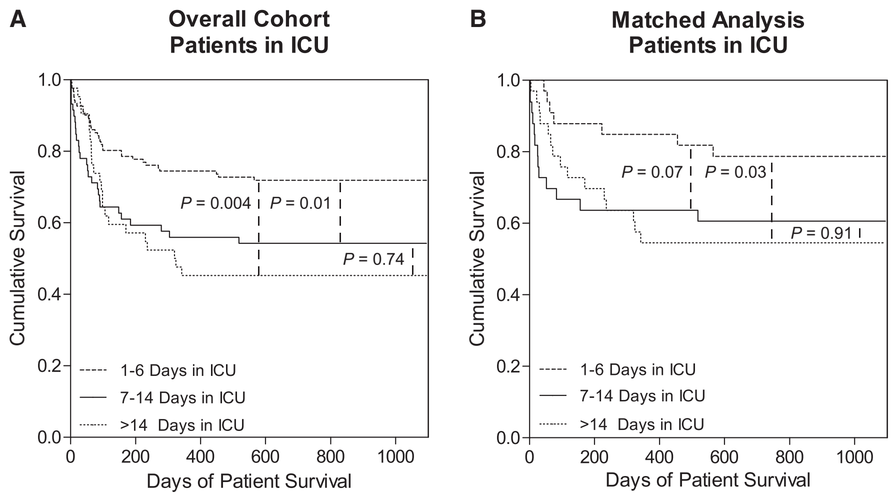

FIG. 4. Kaplan-Meier survival analysis for patients hospitalized in the ICU prior to transplantation by number of ICU days directly before transplantation. (A) Unmatched analysis (overall cohort) and (B) after propensity score–matched analysis (matched cohort). The matching covariates are recipient age, recipient BMI, recipient sex, laboratory MELD score, indication for LT, MELD exceptional status, HU status, retransplantation, split organ, CIT, donor age, donor BMI, and donor sex. Patients in the unmatched analysis: 1-6 days in the ICU (group 1, n = 124), 7-14 days in the ICU (group 2, n = 60), and >14 days in the ICU (group 3, n = 42). Trends for the unmatched analysis: overall trend, $P = 0.006$; group 1 versus group 2, $P = 0.01$; group 1 versus group 3, $P = 0.004$; and group 2 versus group 3, $P = 0.74$. Patients in the matched analysis: all groups, n = 32. Trends for the matched analysis: overall trend, $P = 0.10$; group 1 versus group 2, $P = 0.07$; group 1 versus group 3, $P = 0.03$; and group 2 versus group 3, $P = 0.91$.

TABLE 5. Characteristics for Patients in ICU Before LT Classified by Length of ICU Stay

				P Value			
	1-6 ICU Days (n = 124)	7-14 ICU Days (n = 60)	>14 ICU Days (n = 42)	All Groups	1-6 Days Versus 7-14 Days	1-6 Days Versus >14 Days	7-14 Days Versus >14 Days
Age at LT, years	48.5 ± 12.7	50.1 ± 12.2	50.7 ± 11.1	0.53	0.42	0.33	0.81
Sex, male	70 (56.5)	31 (51.7)	23 (54.8)	0.83	0.54	0.85	0.76
BMI, kg/m^2	25.9 ± 4.8	25.5 ± 5.6	24.7 ± 4.7	0.43	0.65	0.18	0.46
Laboratory MELD	35 (24-40)	35.5 (28.5-40)	35 (26.75-39)	0.67	0.37	0.76	0.67
Match MELD	35 (24-40)	36 (29.75-40)	35 (26.75-39.25)	0.52	0.26	0.71	0.54
Exceptional MELD	1 (0.8)	3 (5.0)	4 (9.5)	**0.02**	0.21	**0.004**	0.37
Retransplantation	50 (40.3)	30 (50.0)	30 (71.4)	**0.002**	0.21	<**0.001**	**0.03**
HU status	78 (62.9)	29 (48.3)	21 (50.0)	0.11	0.06	0.14	0.87
Dialysis	45 (36.3)	40 (66.7)	29 (69.0)	<**0.001**	<**0.001**	<**0.001**	0.80
Ventilation	50 (40.3)	26 (43.3)	24 (57.1)	0.20	0.78	0.11	0.09
Catecholamine therapy	59 (47.6)	30 (50.0)	28 (66.7)	0.30	0.91	0.15	0.17
Waiting time, days	2.0 (1.0-6.8)	3.0 (2.0-12.8)	3.5 (2.0-24.0)	0.08	0.18	**0.04**	0.27
Posttransplant ICU stay, days	19.0 (9.2-46.8)	22.5 (10.0-44.0)	53.5 (27.2-97.2)	<**0.001**	0.85	<**0.001**	<**0.001**
Posttransplant hospital stay, days	44.5 (26.0-74.2)	39.0 (22.5-60.5)	64.5 (44.8-99.0)	**0.001**	0.35	**0.001**	**0.001**

NOTE: Data are given as mean ± SD, median (IQR), or n (%). Bold indicates significance at $P < 0.05$. The data presented here correspond to Fig. 4A.

TABLE 6. Significant Risk Factors in Multivariate Cox Regression for 1-Year Patient Survival After LT

	HR	95% CI	*P* Value
Retransplantation	2.18	1.55-3.07	<0.001
Serum creatinine	1.15	1.06-1.26	<0.001
Days in hospital prior LT	1.02	1.01-1.04	0.001
Dialysis prior LT	1.97	1.41-2.76	<0.001
Catecholamine therapy	2.13	1.46-3.13	<0.001
Surgery time	1.003	1.001-1.004	<0.001
DRI	1.42	1.16-1.74	0.001

between patients hospitalized in a RW and in ICU prior to LT ($P = 0.10$).

The results of Cox regression analysis for 1-year patient survival are presented in Table 6 and Supporting Table 8. Days hospitalized before LT showed a hazard ratio (HR) of 1.02 (95% confidence interval [CI], 1.01-1.04) in the multivariate analysis. Further parameters influencing survival were retransplantation (HR, 2.18; 95% CI, 1.55-3.07), serum creatinine values before LT (HR, 1.15; 95% CI 1.06-1.26), catecholamine therapy prior to LT (HR, 2.13; 95% CI, 1.46-3.13), dialysis prior to LT (HR, 1.97; 95% CI, 1.41-2.76), surgery time (HR, 1.003; 95% CI, 1.001-1.004), and donor risk index (DRI; HR, 1.42; 95% CI, 1.16-1.74).

Discussion

Although it is common knowledge that pretransplant hospitalization may negatively affect post-LT outcomes, this is the first study to demonstrate the substantial influence of the length of pretransplant hospitalization status on posttransplant survival. Hospitalization before LT and the length of stay in the ICU prior to LT correlates significantly with decreased patient survival after LT and is a strong predictor of longterm results. These results were independent of other relevant risk factors (including recipient age, laboratory MELD score, retransplantation, donor age, CIT, and others).

Very few published studies have demonstrated a direct correlation between pre-LT hospitalization status and longterm outcomes.[7,16] Bittermann et al. described a decreased survival for patients hospitalized in the ICU compared with those in a RW.[16] Sibulesky et al. also described a reduced survival after LT for patients in the ICU; however, these findings were influenced by patients receiving donation after circulatory death grafts and were not consistent when analyzing only regular donation.[17] In a third study, ICU patients only showed a tendency for decreased survival, but this was not found to be significant.[22] Duration of hospital stay directly before transplantation and its correlation with posttransplant survival was not analyzed in these studies. In a more recent work by Bittermann et al., all hospital stays in the 3 months before LT were evaluated; however, the primary endpoint was not total survival but days alive out of hospital. Nevertheless, they described similar results to our study, as the number of days alive out of hospital in the first year after LT decreased with increasing days spent in hospital 90 days before LT.[23] None of the previously mentioned studies evaluated patients switching between these 3 groups. Therefore, we evaluated whether analyzing the groups by hospitalization status defined only at the time of LT is reasonable. We could demonstrate that patients can be considered outpatients even if they had hospital admissions in their 30-day history (see Fig. 2B). This also suggests that it is reasonable to account for patients who had been hospitalized more than a month ago and, afterward, had been stable at home for at least a month as ambulatory patients. Similarly, we highlighted that patients from RW have the same outcome independent of prior ICU stays.

Hence, the evaluation of the hospital admission directly prior to LT seems to be sufficient to predict posttransplant survival, and hospitalization status and duration should be included in decision-making processes for whether to accept an organ for LT or not.

Differences in short-term survival between patients transplanted from a RW versus from an ICU were seen by trend; however, they did not reach statistical significance, and no differences were seen for longterm survival. As mentioned previously, differences between those 2 groups were found in a larger study with >50,000 transplantations from UNOS between 2002 and 2013.[16] This can be explained by differences in the study group size and the severity of illness. Frequencies of dialysis, ventilation, and catecholamine therapy before LT were increased in our cohort compared with UNOS data. In addition, overall rates of hospitalization were higher in our study (United States, 24.6%; Berlin, 35.5%) as were ICU recipients (United States, 8.1%; Berlin, 21.2%), highlighting differences in the overall recipient collective and donor availability in these countries. Interestingly, median laboratory MELD score at LT was similar in both groups (United States, 18; Berlin, 17), emphasizing the value of hospitalization before LT and its duration as an independent risk factor. These differences as well as low organ donation rates and higher rates of marginal donors in Germany could also explain the relatively low overall survival of our study group and other German transplant centers in comparison to international data.[24-26]

Patients with high MELD scores, who are prioritized with organ offers, are prone to poorer posttransplant outcomes.[7,27] Different scores exist to predict posttransplant survival, including the BAR score, the SOFT score, and DRI.[4,7,11] However, these scores are yet to be prospectively evaluated, especially because existing outcome scores are complex with multiple parameters, with several either being unavailable at allocation (eg, CIT) or partly subjective (grade of encephalopathy or ascites) and, therefore, impractical.[7,11,28]

Certainly, there are other criteria such as pre-LT frailty or sarcopenia that can estimate patients' overall health status and are potentially treatable risk factors and predictors for patient survival.[13,29] Unfortunately, their assessment limits their applicability in organ allocation because they cannot be updated easily. For example, CT of muscle mass would be expensive and would put patients at risk of adverse effects from the contrast agent. Assignment of the Liver Frailty Index[30] would be less time-consuming but would still require examination by trained personnel at the transplant center. In addition, the health status of listed patients can deteriorate rapidly, and frequent reevaluation would be necessary for use in allocation.

The consideration of the question "when is a patient too sick for LT" becomes increasingly relevant, especially given the growing number of indications for LT.[31] In a study by Petrowsky et al., factors for futile outcome in highest acuity recipients (MELD score ≥40) were analyzed, and it was found that MELD score but also pretransplant septic shock, cardiac risk, and comorbidities were important predictors of such futile outcomes.[32] In our analysis, not unexpectedly, HU status patients were predominantly in the ICU group. However, because we did not observe a difference between non-ICU and ICU hospitalized patients regarding survival, there was no reason to exclude this cohort from the analysis. Pretransplant hospitalization represents a pragmatic surrogate parameter for a wait-listed patient's general health status. Hospitalization indicates whether the sum of pathological conditions and comorbidities are compensated or not. In addition to this global health information, hospitalization status can be assessed easily at any time and monitored using health service documentation. Pre-LT hospitalization is included in existing outcome scores, such as the SOFT score or the Net Benefit Model, but it is only used as a dichotomous variable at the time of LT without regard to the time spent in the hospital.[7,33] According to our data, we would recommend that patients who have spent more than 1 week in the ICU within the last 30 days prior to organ offer should be evaluated very carefully.

Lynch et al. recently reported similar findings in the context of kidney transplantation. Higher numbers of inpatient days before transplantation were associated with lower graft and recipient survival. Although the duration of observation differed with respect to the pretransplantation listing time, these results emphasize the value of pretransplant hospitalization as an outcome predictor in the context of solid organ transplantation.[34]

Certainly, the question arises of why hospitalization status and duration have such a dramatic effect on post-transplant outcomes. First, it certainly is an indicator for worse overall health status. Second, it is well known that the hospital is the most relevant place to acquire infections, especially with resistant bacteria and fungi. In particular, during the early time after LT, infections increase mortality in LT recipients.[35,36] Even if this might be considered a bias in our analysis, it is a matter of fact and does not change the result: hospitalization is detrimental for post-LT outcomes.

This study has several limitations. First, this is a retrospective analysis from a single center. Although data concerning hospitalization in our institution were available for all patients, the decision of hospital or ICU admission is not entirely objective and always depends on the assessment of the attending physician, the patient's wish, and sometimes organizational circumstances.

In our study, we included all consecutive LTs, whereas other studies excluded patients receiving retransplantation, patients with HU status, or combined liver-kidney transplantations. Our approach may reduce generalizability of the results for particular subgroups, but exclusion of these groups precludes findings about critically ill patients in which transplant outcome is an even more important question. Although former studies did not investigate this topic in detail, their results indicated similar results. Therefore, we conclude that our findings can be generalized despite differences between health care systems.

In conclusion, in times of organ shortage and rising numbers of critically ill recipients, outcome-based parameters should be emphasized for whether to perform an LT or not. Hospitalization status and duration before transplantation are valuable and easily available predictors for patient survival after LT and should be routinely included in the process of organ acceptance in LT. In particular, patients with a prolonged stay in the ICU should undergo interdisciplinary evaluation before the acceptance of organ offers to improve the benefit of scare donor grafts.

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