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Risk Factors for High Mortality on the Liver Transplant Waiting List in Times of Organ Shortage: A Single-Center Analysis

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Background: Germany has the highest rate of patients dying or becoming unfit for transplant while waitlisted within the Eurotransplant region. Therefore, the aim of the current study was to analyze mortality as well as risk factors for mortality of candidates listed for liver transplantation at our center.

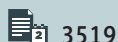
Material/Methods: Between 01/2011 and 12/2013, 481 adult patients were listed for primary liver transplantation (LT) at a single German center. Clinical and laboratory parameters were prospectively collected and retrospectively analyzed by univariable and multivariable logistic regression and Cox proportional hazards.

Results: The mean model for end-stage liver disease (MELD) score of all liver transplant waitlist registrants (52.4 years, 60.1% male) was 16.9 (± 10.2) at time of listing, with 10% of the listed patients having a MELD score of >32 . After waitlisting, 133 (27.7%) candidates died within the follow-up period. Three-month-survival after listing for transplantation was 89% for patients ultimately receiving LT vs. 71.2% that did not receive LT ($p < 0.001$). Multivariable analysis identified clinical parameters such as ICU treatment, preceding abdominal surgery, variceal bleeding, and ascites, as well as hydropic decompensation, as independent risk factors for waitlist mortality.

Conclusions: Consideration of independent risk factors of mortality within the MELD-based allocation system potentially improves assessment of individual urgency and might improve utilization of available organs.

MeSH Keywords: Liver Transplantation • Mortality • Waiting Lists

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Background

Organ shortage remains the Achilles heel of transplantation medicine. Waiting lists have been established to rank candidates, with the ultimate goal of improving outcomes after transplantation, based on urgency and expected success following liver transplantation. Over time, the criteria of organizing these lists have been changed and improved, resulting in the establishment of the model of end-stage liver disease (MELD)-based organ distribution. The MELD-based allocation system was established in Germany in December 2006. Since the majority of European countries have adopted the MELD-score in 2006–2007, the proportion of patients with a high MELD (>30) at time of transplantation has almost doubled.

Even though waitlist mortality decreased from 20% to approximately 10% [1], outcome following liver transplantation has deteriorated in Germany and Europe, with an average 1-year survival rate of about 75–80% [2,3]. This is largely due to the high percentage of patients being transplanted with a lab-MELD of >30.

In a recent analysis of adult liver allocation within the Eurotransplant region, Germany had the highest rate of patients (26%) either dying or becoming unfit for transplantation while waitlisted for liver transplantation [4]. In contrast, Croatia has a relatively low rate of patients being removed from the waiting list (8%).

Besides the implementation and adaptation of allocation mechanisms, scarcity of organs still plays a dominant role for outcomes of candidates on the waiting list. Patients remain longer on the waiting list, subsequently developing progressive liver disease, resulting in higher mortality rates while waitlisted. Patients present a constant increase in the MELD threshold until finally undergoing transplantation. In fact, patients in Germany have the highest median lab MELD (19) at time of transplant among the 7 countries within the Eurotransplant region, whereas patients in countries such as Hungary present the lowest median lab MELD (13) at time of transplantation [4].

When comparing rates of organ donation per million population (pmp), numbers for organ donation in Germany are very low, being 10.9 in 2013 and 10.8 in 2015 [4]. These numbers stand in sharp contrast to other European countries, where donation rates were remarkably higher (United Kingdom 20.8 pmp, France 25.5 pmp, Spain 35.1 pmp in 2013). Spain, as a worldwide leading country, steadily increased the number of organ donors to above 40 per million population within the past 15 years [5,6]. Unfortunately, the rate of organ donors has faced a constant decline in Germany, and has dropped about one-third from 2010 to 2017, being 797 in 2017 [7–10].

Considering the negative trend of organ donation in Germany in the past decade until 2017, we aimed to analyze waitlist mortality and to identify risk factors for waitlist mortality of patients registered for liver transplantation between January 2011 and December 2013 at our center.

Material and Methods

Study population

We performed a retrospective single-center cohort study of all liver transplant candidates added to our liver transplantation waiting list from January 2011 to December 2013 at the University Hospital of Essen, Germany. Follow-up was carried out until December 2014. Of these, patients <18 years of age and patients listed for combined organ transplantations, as well as living donor liver transplantations, were excluded. Relevant data were recorded from our center's database, as well as the Eurotransplant International Foundation database. Clinical and laboratory parameters were prospectively collected and retrospectively analyzed. This study was approved by the local ethics committee (16-6981-BO, 14.06.2016).

Parameters

For each study subject, the following parameters were recorded and analyzed:

Patient demographics: Gender, age, height, weight, BMI, blood type, type of health insurance (private versus non-private).

Underlying disease and waitlist parameters were: underlying liver disease, hepatocellular carcinoma, Child-Pugh-score, lab MELD, exceptional MELD, MELD at listing, MELD at graft removal, status 1 listing, and number of declined organ offers.

Complications of liver disease while waitlisted were: dialysis, intensive care unit (ICU) treatment, mechanical ventilation, inotropic support, hydropic decompensation, ascites, encephalopathy, hepatorenal syndrome, and variceal bleeding.

Comorbidities at time of listing were: coronary artery disease, history of myocardial infarction, arterial hypertension, cardiac insufficiency, diastolic dysfunction, cardiac valvular dysfunctions, pulmonary hypertension, pulmonary diseases, diabetes, preceding abdominal surgery, and portal vein thrombosis.

Laboratory values at listing were: international normalized ratio (INR), bilirubin, creatinine, estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal disease (MDRD) equation, serum sodium, serum albumin, serum protein, and thrombocytes.

Statistical analysis

Data are expressed as mean and standard deviation, as well as median and range, where appropriate. Patient survival was calculated using the Kaplan-Meier method and compared with the log-rank test. Univariable and multivariate regression analyses were performed with binary logistic regression and Cox proportional hazard models. Variables that were statistically significant by univariate analyses were subsequently evaluated by multivariate analysis. Multivariate cox proportional hazards analysis were carried out with backward variable selection. Odd ratios and risk ratios were obtained from regression models.

$P < 0.05$ was considered statistically significant. Statistical analyses were performed using JMP (version 10.0.0 SAS, SAS Institute, Inc., Cary, NC) and SPSS (version 24.0.0.0, IBM, Armonk, NY).

Results

Study population

During the study period, 574 patients were newly added to the waiting list or newly registered for liver transplantation at our institution. Of these, 70 patients were younger than 18 years old, 4 patients were listed for combined transplantations, and 16 patients underwent living donor liver transplantation. These patients were excluded from the trial, so that 481 patients remained for further analysis. Of the remaining 481 candidates, 289 underwent liver transplantation (including 3 living donor liver transplantations and 3 domino liver transplantations), whereas 192 candidates did not receive liver transplantation during the study period.

Patient demographics

The mean age at listing for liver transplantation was 52 ± 10.4 years. The youngest patient in this study was 18 years old, while the oldest patient listed for transplantation was 75 years of age. Most candidates were male (289 (60.1%)). Mean body height was 173 ± 9.7 cm (range 146–204 cm), mean body weight was 77.5 ± 18.6 kg, and the resulting BMI was 25.8 ± 5.1 kg/m². Six patients had a BMI > 40 kg/m², and 27 patients had a BMI < 18.5 kg/m². We noticed a typical blood type distribution in our cohort: A=44.7%, O=36.8%, B=12.9%, AB=5.7%. Only 14.4% of candidates had private health insurance.

Disease and waiting list data

Underlying causes for end-stage liver disease were alcoholic steatohepatitis in 98 (20.4%), hepatitis C in 55 (11.4%), primary sclerosing cholangitis in 32 (6.7%), hepatitis B or D or

coinfection in 19 (4%), and non-alcoholic steatohepatitis (NASH) in 15 (3.1%) individuals. Other causes of end-stage liver disease were present in 167 (34.7%) patients. Of all patients listed for liver transplantation, 98 (20.4%) had hepatocellular carcinoma.

The Child-Pugh-Score was not available retrospectively for all patients. However, we identified 57 patients (20.4%) with a Child-Pugh-Score A, 161 (57.7%) patients with Child-Pugh-Score B, and 62 patients (22.2%) with Child-Pugh-Score C.

The mean MELD score at time of listing for liver transplantation was 16.9 ± 10.2 . At time of transplantation, the mean MELD score was 22.3 ± 9.3 . In our cohort, 47 (9.8%) patients were listed with status 1. Of these, 40 (85.1%) underwent liver transplantation during the observation period.

The median waiting time for all patients was 214 (0–1224) days. During the study period, a total of 2011 organ offers were documented for all 481 patients. Of these offers, 1714 (85.2%) were declined, and the remaining 289 organs offered (14.8%) were accepted and transplanted. The median number of organ offers per patient was 2 (range 1–109). The most frequent reasons for organ decline were poor quality and size mismatch (51.1% and 28.8%, respectively). The mean and median time until liver transplantation was 214 and 259 days, respectively.

The most frequent cause of death for waitlisted patients was infection (39%).

Complications of liver disease in waitlist candidates

After waitlisting, typical complications of end-stage liver disease occurred in the majority of patients and included: ascites ($n=256$; 53.2%) and encephalopathy ($n=156$; 32.4%). Hepatorenal syndrome was observed in 73 (15.2%) patients. In 63 (13.1%) cases, hydroptic decompensation occurred. Bleeding from esophageal varices was observed in 55 (11.4%) patients during the waiting period. ICU treatment after listing for liver transplantation was necessary in 54 (11.2%) cases, 35 (7.3%) of which required inotropic support. Mechanical ventilation was necessary in 39 cases (8.1%) and hemodialysis was required in 55 (11.4%) patients.

Of all candidates listed for liver transplantation at our center, 28 (5.8%) patients were diagnosed with complete portal vein thrombosis, while a partial thrombosis was seen in 12 (2.5%) patients.

Comorbidities of waitlisted candidates

Cardiovascular comorbidities were common among waitlist candidates. Of the 481 patients listed, 225 (46.8%) had at least 1 cardiovascular comorbidity. Arterial hypertension was

the most prevalent cardiovascular disease (26%), coronary artery disease was present in 12.5% of all patients, and 2.7% had suffered a myocardial infarction in the past. Valvular stenosis or insufficiency \geq II° were observed in 8.5%. Due to heterogeneity of these diseases, we abstained from further discrimination and analysis. Diastolic dysfunction was diagnosed in 13.5% of patients and pulmonary hypertension was diagnosed in 6% of patients.

Pulmonary comorbidities were documented in 66 (13.7%) cases. Asthma and COPD were seen in 11 (2.3%) and 26 (5.4%) patients, respectively. Other pulmonary comorbidities were very heterogeneous, and, due to the low frequency, are not specified further.

Diabetes mellitus was very common. Of the 115 patients who had a history of diabetes, 110 (22.9%) had diabetes type 2 and 5 (1%) had diabetes type 1.

Previous abdominal surgery had been performed in 140 (29.1%) patients prior to listing. Most of these were minor abdominal interventions (41.3%), 23.3% were classified as intermediate interventions, and 35.4% as major interventions.

Factors predicting the chance of being transplanted in waitlisted candidates

To identify predictive factors for waitlisted candidates to be transplanted, we first compared candidates that received a liver transplantation with candidates that remained on the waiting list during the entire observation period (Table 1). Univariate analysis unveiled 18 factors that were significantly different between the 2 groups. We then performed multivariate logistic regression using the above-mentioned factors, and found 6 variables that were significantly different and associated with either receiving or not receiving a liver transplantation (Table 2). ICU treatment, previous abdominal surgery, hepatorenal syndrome, esophageal variceal bleeding, and cardiac diastolic dysfunction were identified as independent predictors for waitlisted patients to not receive a liver transplantation (Table 2). In contrast, height was associated with a likelihood of actually receiving a transplant.

Factors predicting the risk of mortality in waitlisted candidates

Having identified independent risk factors for candidates not to proceed to transplant (ICU treatment, preceding abdominal surgery, hepatorenal syndrome, esophageal variceal bleeding, cardiac diastolic dysfunction) and a factor that was associated with a higher chance of being transplanted (height), we now aimed to investigate characteristics that were associated with death on the waiting list.

Clinical variables were compared between candidates that either died and those candidates who stayed alive during the observation period (Table 3). Here, univariate analysis demonstrated 21 demographic and clinical factors discriminating between the 2 groups (Table 3). Subsequent multivariate logistic regression was performed with factors significantly associated with death on the waiting list in the preceding univariate analysis. Interestingly, the factors found to be associated with a higher mortality were previously found to be associated with a lower chance of being transplanted.

MELD score at time of listing ($p=0.01$), ICU treatment ($p=0.001$), preceding abdominal surgery ($p=0.01$), variceal bleeding ($p=0.04$), and ascites ($p=0.001$), as well as hydropic decompensation ($p=0.03$), were delineated as independent predictors for death on the waiting list (Table 4). Again, shorter height was an independent factor for an unfavorable outcome and increased mortality ($p=0.03$).

Next, in a time-dependent manner using Cox proportional hazard analysis, we analyzed patient survival after listing for liver transplantation (Tables 5, 6). Univariate analysis of factors used for the subsequent multivariate analysis are depicted in Table 5. Here, multivariate analysis demonstrated that 4 factors were independently associated with time-dependent mortality: age ($p=0.01$), MELD score at listing ($p<0.001$), necessity of ICU treatment ($p<0.001$), and history of myocardial infarction ($p=0.03$). Liver transplantation itself was associated with reduced mortality for waitlisted candidates ($p<0.001$) (Table 6).

Mortality

We next assessed the mortality rates of waitlisted patients that proceeded to liver transplantation ($n=289$) versus those candidates that remained on the waiting list without ever being transplanted ($n=192$) during the observation period.

During the study period, a total number of 133 (27.7%) patients died after being registered as candidates for liver transplantation. Kaplan-Meier analysis of all patients on the waiting list demonstrated 30-day, 3-month, 6-month, and 1-year survival rates of 89.7%, 81.5%, 76.4%, and 64.9%, respectively (Figure 1).

When comparing candidates who received a transplant versus those who did not, survival rates for patients undergoing liver transplantation were 94.3%, 88.6%, 86.1%, and 78.4% after 30 days, 3 months, 6 months, and 1 year, respectively. Those survival rates were significantly better compared to those in patients who did not receive liver transplantation (83.5%, 71.6%, 61.4% and 45.6% after 30 days, 3 months, 6 months, and 1 year, respectively) ($p<0.001$) (Figure 1).

Table 1. Clinical parameters and predictive factors for liver transplantation during waiting for liver transplantation, univariable.

Variable	LT n=289	No LT n=192	p-Value
Gender (Male)	179 (62%)	110 (57%)	0.11
Height (cm)	174±9.7	171±9.5	0.001
Weight (kg)	79.3±18.1	74.8±19	0.01
BMI (kg/m ²)	25.7±5.3	25.9±4.7	0.23
Blood type	A=42.3% O=36.8% B=12.3% AB=8.6%	A=47.1% O=36.8% B=13.6% AB=2.6%	0.11
Coronary artery disease	33 (11.4%)	27 (14.1%)	0.35
History of myocardial infarction	9 (3.1%)	4 (2.1%)	0.43
Cardiac valvular disease	11 (3.8%)	30 (15.6%)	<0.001
Arterial hypertension	84 (29.1%)	41 (21.4%)	0.06
Diastolic dysfunction	29 (10%)	35 (18.2%)	0.01
Pulmonary hypertension	13 (4.5%)	16 (8.3%)	0.09
Pulmonary diseases	30 (10.4%)	36 (18.8%)	0.79
Diabetes mellitus	82 (28.4%)	33 (17.7%)	0.53
Portal vein thrombosis	11 (3.8%)	17 (8.9%)	0.56
Preceding abdominal surgery	74 (25.6%)	66 (34.4%)	0.01
MELD at listing	16±9.9	18.4±10.7	0.02
Child Pugh	A=35 (21.5%) B=94 (57.7%) C=34 (20.8%)	A=22 (18.8%) B=67 (57.3%) C=28 (23.9%)	0.66
Waiting time (days)	74 (0–1216)	216 (1–109)	<0.001
Declined organ offers	2 (3–75)	2 (1–109)	0.14
ICU treatment	23 (8%)	31 (16%)	0.01
Mechanical ventilation	15 (5.2%)	24 (12.5%)	0.01
Inotropic support	15 (5.2%)	20 (10.4%)	0.04
Dialysis	26 (9%)	29 (15.1%)	0.045
Hepatorenal syndrome	27 (9.3%)	46 (24%)	<0.001
Variceal bleeding	26 (9%)	29 (15.1%)	0.045
Encephalopathy	72 (24.9%)	84 (43.8)	<0.001
Ascites	140 (48.4%)	116 (60.4%)	0.01
Hydropic decompensation	26 (12.1%)	28 (14.6%)	0.04
Status-1 listing	40 (13.8%)	7 (3.7%)	0.01
HCC	54 (18.7%)	44 (22.9%)	0.3
Private health insurance	49 (18%)	16 (9%)	0.17

HCC – hepatocellular carcinoma; LT – liver transplantation; MELD – model for end-stage liver disease.

Table 2. Predictive factors for “death on waiting list” while waiting for liver transplantation, univariable.

Variable	Odds ratio (95%-CI)	p-Value
Height	1.03 (1.01–1.05)	0.002
Hepatorenal syndrome	0.31 (0.18–0.54)	0.001
Variceal bleeding	0.47 (0.25–0.86)	0.02
ICU treatment	0.51 (0.27–0.95)	0.03
Diastolic dysfunction	0.46 (0.28–0.9)	0.02
Preceding abdominal surgery	0.74 (0.57–0.97)	0.03

ICU – intensive care unit.

Patients dying while on the waiting list had a median waiting time of 102 (0–946) days, compared to median 111 (0–1224) days for patients not dying on the waiting list ($p=0.06$).

Discussion

We found high mortality rates for patients waitlisted for liver transplantation at a single German center: 23.6% at 6 months and 35.1% at 1 year after initial listing. Recent data confirm that this is a national problem, with 26% of adult liver transplant candidates ultimately being removed from the waiting list due to death or deterioration of health [4].

However, patients who underwent liver transplantation had outcome results comparable to other transplant centers within the Eurotransplant region [11–13].

One reason for the high mortality rate is the relatively high labMELD score at time of transplantation.

The mean MELD score of our patients at time of listing was 16.9 ± 10.2 and 22.3 ± 9.3 at time of transplantation. This current score lies above the mean MELD of recipients in 7 major transplant centers after introduction of the MELD system in Germany (December 2006 to December 2007), which at that time was 19.6 ± 10 at time of liver transplantation [14]. This reflects the constant increase of MELD for waitlisted patients in Germany [1]. As mentioned before, patients in Germany have the highest median lab MELD (19) at time of transplant among the Eurotransplant region [4].

Besides the implementation and adaptation of allocation mechanisms, severe organ shortage is another reason for high mortality rates and thus still plays a dominant role for outcomes of candidates on the waiting list. The constant increase in the MELD threshold is a challenge, since it is a consequence of increased time for disease progression and complications to occur, ultimately leading to increased drop-out rates. The reasons for a decline and stagnation of organ donations in Germany until

2017 are multifactorial. First, the uncovering of systematic irregularities within 2 major transplant centers shook the confidence in the allocation system and has resulted in considerably reduced liver transplantations and registrations for liver transplantation thereafter [7]. Second, Germany follows an “informed consent” policy for organ donation, which stands in contrast to the “presumed consent” policy. Also, the German transplant legislation prohibits the inclusion of donations after cardiocirculatory death. Apart from the above-mentioned reasons, continuing medical advances in the field of critical care medicine, palliative care, and neurosurgery render fewer candidates ultimately suitable for donation [3].

The number of deceased donors used for transplant per million population has declined by 7.8% to 9.3 pmp in Germany from 2016 to 2017, which stands in contrast to relatively stable numbers in Austria (–1%, 23.5 pmp in 2017) [9]. In 2017 there were 2232 potential organ donors reported in Germany, with an average of 18.8 reports made per hospital [10]. In the United States, numbers of donations after brain death (DBD) and after circulatory death (DCD) increased in 2016 to 8287 and 1684, respectively, continuing a steady increase since 2010. Two potential reasons for the growth in donors and numbers of deceased donor transplants in the United States were given: the rising number of deaths of young individuals due to the opioid epidemic, and the increasing use of organs from DBD donors [15].

The most effective approach to reduce waitlist mortality would be to increase the number of transplantable organs. Based on the current status, several strategies can be implemented in order to increase the number of donor organs in Germany. First, the increase of utilization of optimal donor organs, as in the case of living related liver transplantation, might be an option to provide these patients with a donor organ early after listing, while in a relatively stable physical condition. The utilization of living donors, for carefully selected recipients, has been demonstrated to be feasible and effective and is associated with a low risk for the donor. Second, declined organ offers could be reassessed and utilized. However, the number

Table 3. Predictive factors for “death on waiting list” while waiting for liver transplantation, univariable.

Variable	Death on waiting list n=133	Alive n=348	p-Value
Age at listing	52.4±10.1	52.4±10.4	0.12
Gender (Male)	76 (57.1%)	213 (61.2%)	0.45
Height (cm)	170±9.6	174±9.6	<0.001
Weight (kg)	73.4±18.6	79±18.4	0.003
BMI (kg/m ²)	25.9±4.7	25.7±5.2	0.15
Coronary artery disease	18 (13.5%)	42 (21.1%)	0.27
History of myocardial infarction	3 (2.3%)	10 (2.9%)	0.64
Cardiac valvular disease	21 (15.8%)	20 (5.8%)	0.002
Arterial hypertension	28 (21.1%)	97 (27.8%)	0.12
Diastolic dysfunction	21 (15.8%)	43 (12.4%)	0.25
Pulmonary hypertension	12 (9%)	17 (4.9%)	0.1
Pulmonary diseases	34 (25.6%)	53 (15.2%)	0.8
Diabetes mellitus	29 (21.8%)	87 (25%)	0.48
Portal vein thrombosis	15 (11.3%)	25 (7.2%)	0.2
Preceding abdominal surgery	41 (30.8%)	99 (28.5%)	0.01
MELD at listing	21.4±10.9	15.4±9.5	<0.001
Child Pugh	A=12 (16.00%) B=40 (53.3%) C=23 (30.7%)	A=45 (22%) B=121 (59%) C=39 (19%)	0.17
Waiting time (days)	102 (0–946)	111 (0–1224)	0.06
Declined organ offers	2 (1–96)	2 (1–109)	0.14
ICU treatment	31 (23.3%)	23 (6.6%)	<0.001
Mechanical ventilation	24 (18%)	15 (4.3%)	<0.001
Inotropic support	20 (15%)	15 (4.3%)	<0.001
Dialysis	28 (21%)	27 (7.8%)	<0.001
Hepatorenal syndrome	40 (30.1%)	33 (9.5%)	<0.001
Variceal bleeding	23 (17.3%)	32 (9.2%)	0.02
Encephalopathy	68 (51.1%)	88 (25.3%)	<0.001
Ascites	89 (66.9%)	167 (48%)	<0.001
Hydropic decompensation	30 (22.6%)	33 (9.5%)	<0.001
Status-1 listing	7 (5.3%)	30 (8.6%)	0.22
HCC	24 (18.1%)	74 (21.2%)	0.6
Private health insurance	10 (8.4%)	55 (16.7%)	0.19

HCC – hepatocellular carcinoma; ICU – intensive care unit; MELD – model for end-stage liver disease.

Table 4. Predictive factors for “death on waiting list” during waiting for liver transplantation, multivariable.

Variable	Odds ratio (95%-CI)	p-Value
Height	0.96 (0.93–0.98)	0.03
Variceal bleeding	2.1 (1.05–4.22)	0.04
ICU treatment	3.58 (1.68–7.63)	0.001
Ascites	2.39 (1.42–4.1)	0.001
Hydropic decompensation	2.1 (1.1–4.0)	0.03
Preceding abdominal surgery	1.47 (1.1–1.9)	0.01
MELD at listing	1.04 (1.01–1.06)	0.01

ICU – intensive care unit; MELD – model for end-stage liver disease.

Table 5. Factors for time-dependent mortality during waiting for liver transplantation, univariable.

Variable	p-Value	Variable	p-Value
Liver transplantation (yes/no)	0.0001	Diastolic dysfunction	0.64
Gender (Male)	0.52	Pulmonary hypertension	0.75
Height (cm)	0.11	Pulmonary disease	0.84
Weight (kg)	0.38	Diabetes mellitus	0.75
Age at listing	0.07	Pulmonary artery thrombosis	0.08
BMI (kg/m ²)	0.97	Preceding abdominal surgery	0.59
Private health insurance	0.24	MELD at listing	0.0001
Blood type	0.39	Child-Pugh	0.06
INR at listing	0.0001	Waiting time (days)	0.0001
Bilirubin level at listing (mg/dl)	0.0001	Declined organ offers	0.08
Creatinine level at listing (mg/dl)	0.0001	HCC	0.17
eGFR-MDRD at listing (ml/min/1.73 m ²)	0.02	ICU treatment	0.0001
Sodium level at listing (mmol/l)	0.99	Mechanical ventilation	0.0001
Albumin level at listing (g/dl)	0.001	Inotropic support	0.0001
Total serum protein at listing (g/dl)	0.001	Dialysis	0.0001
Platelet count at listing (μl)	0.001	Hepatorenal syndrome	0.0001
Coronary artery disease	0.26	Variceal bleeding	0.59
History of myocardial infarction	0.04	Hydropic decompensation	0.001
Cardiac valvular disease	0.61	Encephalopathy	0.0001
Arterial hypertension	0.41	Ascites	0.07
Congestive heart failure	0.93	Status-1 listing	0.04

eGFR – estimated glomerular filtration rate; HCC – hepatocellular carcinoma; ICU – intensive care unit; MDRD – Modification of Diet in Renal Disease; MELD – model for end-stage liver disease.

of offered organs were significantly lower in the group of patients dying on the waiting list. Moreover, reasons for the decline were size mismatches or limited organ quality in most

cases. Although organ size match cannot be modified, the utilization of marginal-organs could increase the absolute number of potential grafts. Within the past decade, the introduction of

Table 6. Predictive factors for time-dependent mortality during waiting for liver transplantation, multivariable.

Variable	Odds ratio (95%-CI)	p-Value
Age	1.02 (1.004-1.04)	0.01
History of myocardial infarction	2.41 (1.12-4.54)	0.03
ICU treatment	2.49 (1.59-3.82)	<0.001
MELD at listing	1.06 (1.04-1.08)	<0.001
Liver transplantation	0.28 (0.2-0.39)	<0.001

ICU – intensive care unit; MELD – model for end-stage liver disease.

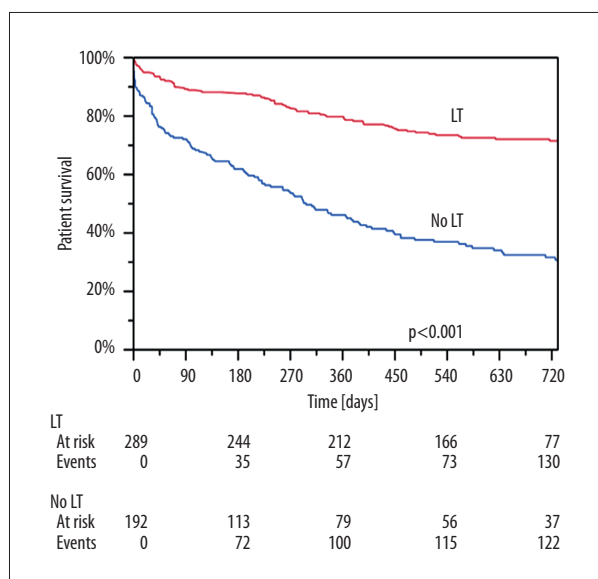


Figure 1. Survival after listing for liver transplantation for patients undergoing liver transplantation (LT) and not undergoing liver transplantation (no LT). LT – liver transplantation.

new (or improved) preservation methods (i.e., organ perfusion models to improve reduced organ quality) has become the focus of attention [16]. Also, the use of split livers could be reassessed as a further source, although it accounts for about 6% of overall deceased donor liver transplant in the past decade [4]. Apart from these strategies, a change of legislation and utilization of DCD donations, which is illegal in Germany, could be another opportunity to address the organ shortage. Also, the change of donation legislation from the “opt-in” system to an “opt-out” system with presumed consent for deceased organ donation be yet another opportunity. The outstanding example of Spain, which has increased donor rates up to 40 per million inhabitants demonstrates that there are solutions that can be implemented.

In the present study, we identified characteristics of waitlisted patients associated with liver transplantation after registration on the waiting list besides the MELD score itself. Body height,

hepatorenal syndrome, variceal bleeding, ICU treatment, diastolic dysfunction, and previous abdominal surgery were associated with a higher chance for proceeding to and receiving liver transplantation. Patients were more likely to be transplanted when they were taller, but were less likely when comorbidities were present. Hepatorenal syndrome, ICU treatment, and diastolic dysfunction significantly elevate the peri- and postoperative risks for the recipients. Previous abdominal surgery most likely prolongs recipient hepatectomy, which prompts a longer cold ischemia time, which in turn is associated with significantly more postoperative complications [17]. Variceal bleeding reflects the severity of portal hypertension, and thus is a surrogate measure for more complicated intraoperative settings. This adds to the risk of the procedure itself, with an increased blood loss during surgery. Patients might have episodes of variceal bleeding while waitlisted, which would decrease the odds for being transplanted in general.

The high mortality among recipients has been placed in an international comparison and discussed in the literature, where the MELD allocation system with a ‘sickest-first’-concept in combination with poor donor organ quality were defined as responsible factors within the Eurotransplant region [16,17]. Besides the MELD score itself, various risk factors and models have been identified and validated for their predictive capacity in liver transplantation over time, which take both recipient and donor variables into account [18]. Among these, the survival outcomes following liver transplantation (SOFT) score [19], the donor model for end-stage liver disease (D-MELD) [20], the balance of risk (BAR) score [21], and risk model by Burroughs et al. [22] all use a combination of donor, recipient, and transplant factors in a single predictive model. The donor risk index (DRI) and the Eurotransplant (ET-DRI) comprise donor and transplant factors [23,24].

The shortage of donor organs is usually assumed to increase the influence of exceptional MELD points and lead to a disproportional advantage of patients with exceptional MELD points compared to other candidates on the waiting list. In the present study, we were not able to delineate such a mechanism. HCC patients, who account for the majority of patients

receiving exceptional MELD points, were equally distributed in the groups of patients undergoing transplantation and patients remaining on the waiting list. Also, the distribution of HCC patients did not differ between patients surviving or dying on the waiting list.

The predominant limitations of the present study are its single-center design and its retrospective nature. Multi-center analyses, and preferably nation-wide analyses performed through a transplant registry, could shed further light on the risk factors involved in waitlist mortality.

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Conclusions

This study delineates a high mortality on the waiting list for liver transplantation candidates at a large-volume transplant center at a time of severe organ shortage. Although risk factors such as high MELD at listing, as well as severe comorbidities, were identified as risk factors for candidates to die while on the waiting list, organ shortage remains the primary cause for and challenge in the current state. Systematic changes in the practice of donation could present a solution to close the gap between the demand and the availability of transplantable organs.

Conflicts of interest

None.