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Original article

Improvement of renal function prior to liver transplantation is not associated with better long-term renal outcome or survival

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ABSTRACT

Introduction and objectives: Since MELD implementation renal impairment in liver transplant (LT) recipients has become of increasing importance. This is the first study evaluating the course of renal function immediately prior to LT as predictor for long-term renal and overall outcome.
Patients and methods: In this retrospective study, 226 adults undergoing LT at the University Medical Center Hamburg-Eppendorf (2011-2015) were included. The impact of renal function over a period of 3 months prior to LT compared to renal function at the day of LT on long-term renal outcome and survival was assessed.
Results: According to GFR at day of LT renal function improved (≥1 CKD stage) in 64 patients (28%), remained stable in 144 (64%) or deteriorated in 18 (8%). Improvement of renal function prior to LT did neither significantly affect 90-day (13% vs. 14%, p = 0.83), nor 5-year post-LT mortality (35% vs. 41%, p = 0.57). 50 patients (22%) with hepatorenal syndrome (HRS) received terlipressin prior to LT, but only 18 (37%) showed prolonged stabilization of renal function (improvement ≥1 CKD stage). Response to terlipressin did neither improve 90-day (p=1), 5-year mortality (p = 0.52) nor long-term renal function (p = 0.843). Nevertheless, need for dialysis pre-LT (59% vs. 34%, p = 0.005) and post-LT (62% vs. 17%, p<0.001) was associated with increased 5-year mortality.
Conclusions: Improvement of renal function immediately prior to LT, either spontaneously or following terlipressin therapy, did neither ameliorate long-term renal outcome nor survival in LT recipients. Future studies need to clarify the impact of terlipressin in HRS on the transplant waiting time in LT candidates.

1. Introduction

Orthotopic liver transplantation (LT) has become a well-established therapeutic option and standard of care for patients with acute or chronic liver failure. Renal dysfunction is frequently observed in liver transplant recipients and represents a major complication regarding long-term outcome and quality of life. As renal function is a major component of the model for end stage liver disease (MELD) score, its implementation for organ allocation increased the rate of LT candidates with renal dysfunction pre LT [1,2]. Calcineurin inhibitors, such as ciclosporine or tacrolimus, which play a key role in immunosuppressive regimens for patients undergoing solid organ transplantation, are able to induce tubular atrophy, interstitial fibrosis and reduce renal blood flow. Therefore, calcineurin inhibitors have undoubtfully been shown to be a central cause of post LT renal insufficiency [3–5]. A large study, assessing the UNOS database, reported a cumulative incidence of CKD 4/5 after LT of up to 20% after 5 years [6]. Development of end stage renal disease after transplantation results in a more than fourfold increased risk of death, as observed in this large cohort of non-renal transplant recipients [6]. Elevated rates of simultaneous liver-kidney transplantation (SLK) and kidney-after-liver transplantation (KALT) are assumed to be the consequence of the induction of the MELD score in the organ allocation system [7,8]. SLK was reported to result in better renal and overall outcome than LT alone [1,9]. Meanwhile, both procedures, SLK and KALT are frequently used options in LT recipients with kidney dysfunction [7,10,11].

Sharma and colleagues investigated renal outcomes after LT in the MELD era: They reported that a reduction of the glomerular filtration rate (GFR) < 60mL/minute at the timepoint of LT seems to be a predictor of post LT chronic renal failure [12]. In contrast, we observed in a cohort of more than 250 LT recipients that very severe renal dysfunction, by means of necessity for postoperative, but not preoperative

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dialysis was associated with reduced 1-year survival [13]. These findings suggest, that in particular the post-operative vulnerable phase is of main prognostic relevance. However, the impact of changes of the renal function immediately prior to LT is still insufficiently understood. This could affect in particular patients with hepatorenal syndrome (HRS), who routinely receive vasoconstrictive drugs (such as terlipressin) combined with albumin as efficacious medical therapy in order to improve renal function [14]. A recent meta-analysis reported that terlipressin can improve not only serum creatinine levels but also short-term survival [14,15]. However, on the other hand improvement of renal function may result in reduction of the MELD score and subsequently, the time on the transplant-waiting list could be negatively affected [16]. Beside this, the effect of terlipressin immediately prior to LT on long-term renal outcome and survival in patients with HRS undergoing LT has not been studied so far.

Therefore, aim of this study was to evaluate the course of renal function immediately prior to LT and assess its impact on long-term renal outcome and overall survival.

1.1. Patients and methods

In this retrospective observational study, 226 adult (age > 18 years) patients were included who underwent LT at the University Hospital Hamburg-Eppendorf between 01/2011 and 12/2015. GFR was determined by the Modification of Diet in Renal Disease (MDRD) formula [17]. Data collection started 3 months prior to LT. For evaluation of the pretransplant renal function the nadir GFR within a time period of 3 month prior to LT and the GFR at the day of transplantation was assessed. Patients receiving combined liver-kidney transplantation were excluded. The study was performed in accordance with the declaration of Helsinki and guidelines of the local ethics committee.

Data regarding demographic characteristics, etiology of underlying liver disease, severity of hepatic impairment (MELD score), severity of kidney dysfunction (CKD stage), use and duration of terlipressin for treatment of HRS, laboratory data as well as necessity of dialysis were collected pre- and postoperatively as well as during long-term follow-up. CKD was defined as stage 1 (GFR ≥90), stage 2 (GFR 60-89), stage 3 (GFR 30-59), stage 4 (GFR 15-29) and stage 5 (GFR <15). HRS was defined as suggested by the current European (EASL) guidelines and patients were treated with terlipressin accordingly. [14] Patients receiving terlipressin were identified via retrospective case analysis of the hospital pharmacy, and the correct indication for terlipressin was confirmed via chart review. Prolonged stabilization of renal function following terlipressin therapy was defined as improvement of at least one CKD stage. Detailed data on presence of infections and acute-on-chronic liver failure (ACLF) prior to LT were available for 146 consecutive patients (65%) undergoing LT between 01/2011 and 12/2014.

Continuous variables were described as median and 25-75% interquartile range (IQR), categorical variables were presented as absolute and relative parameters. Correlation analysis was performed using Spearman's correlation. Continuous variables were compared using Mann-Whitney U test and categorical variables were compared using chi-square tests. Univariate cox hazard regression analysis was performed to determine risk factors of mortality. For estimation of survival, Kaplan- Meier- analysis and Log-Rank - test were performed. For data management and analyses we used Microsoft Excel (Version 16.4), SPSS 27 (SPSS, Inc. Chicago, IL). A p-value of < 0.05 was considered significant.

2. Results

2.1. Patients characteristics

Two hundred twenty-six adult patients (male n = 142, female: n = 84) with a median age of 62 years (IQR 53-68 years) were included in this study. Median follow up post LT was 1491 days. 72 patients (32%) suffered from alcoholic liver disease, 43 (19%) from viral hepatitis, 24 from primary sclerosing cholangitis (11%), 17 (8%) from autoimmune hepatitis, 7 (3%) from non-alcoholic steatohepatitis and 63 (28%) from cryptogenic or other hepatic disease. Hepatocellular carcinoma was documented in 59 (26%) patients. Diabetes was diagnosed in 53 patients (24%) prior to LT, and pre-existing cardiovascular disease in 27 patients (12%). 50 patients (22%) fulfilled the criteria of HRS. At the day of LT 12 patients (5%) were intubated and received mechanical ventilation and 10 patients (4%) were on vasopressor support with norepinephrine. Median stay on the intensive care unit post LT was 8 days (IQR 4-21).

30 patients (13%) had no renal impairment (according to GFR levels ≥90 within a period of 3 months prior to LT), 50 (22%) fulfilled criteria for HRS, whereas 146 (65%) were patients with mixed and overlapping forms of non-HRS AKI, diuretics associated acute or chronic kidney disease as well as acute-on-chronic renal failure.

Confirmed infection (as combination of typical microbiological, laboratory and/or radiological findings) was detected in 26 of 146 patients (18%), whereas clinical suspicion of present infection was observed in 24 (16%) of the patients. In 96 patients (66%), there was no evidence of a present infection. Rate of HRS was significantly higher among patients with suspected or confirmed infection compared to those without (68% versus 32%, p<0.001).

Patient characteristics are shown in table 1 and table 2.

Table 1
Patient characteristics.

No. of patients	226
Age (years)	62 (53-68)
Sex (female), n (%)	84 (37)
BMI	24 (21-28)
MELD	19 (12-30)
Serum creatinine* (mg/dl)	
Creatinine at day of LT	1.3 (0.9-2.6)
Nadir Creatinine within 3 months pre LT	1.5 (1-3.7)
GFR (ml/min)	
GFR at day of LT	56 (26-83)
Nadir GFR within 3 months pre LT	48 (17-77)
HRS *pre LT, n (%)*	50 (22)
Terlipressin response#, n (%)	18/50 (37)
Dialysis pre LT (within 3 months prior to LT), n (%)	40 (18)
Dialysis at day of LT, n (%)	36 (16)
Dialysis post LT, n (%)	99 (44)

Data is shown as absolute number and percent or median and IQR; BMI, body mass index, MELD, model for end stage liver disease; GFR, glomerular filtration rate, HRS, hepatorenal syndrome; LT, liver transplantation; *Serum creatinine in patients with need for dialysis was set at 5.1 mg/dl and GFR as 9.9 ml/min
#Terlipressin response defined as increase of one CKD stage

2.2. Improvement of renal function prior to LT is not associated with improved outcome

Patients were classified according to the nadir GFR value within a period of 3 months prior to LT as CKD 1: 30 patients (13%), CKD 2: 64 (28%), CKD 3: 42 (19%), CKD 4: 40 (18 %) and CKD 5: 50 (22%). Based on the pretransplant GFR directly at the day of LT patients were classified as CKD 1: 46 patients (20%), CKD 2: 61 (27%), CKD 3: 54 (24%), CKD 4: 24 (11%) and CKD 5: 41 (18%).

Compared to the nadir CKD stage 3 months prior to LT the CKD stage had improved at the day of transplantation by at least one stage in 64 patients (28%), whereas renal function remained stable in 144 patients (64%) or deteriorated (one CKD stage) in 18 patients (8%). Improvement of renal function within 3 months prior to LT did neither significantly affect 90-day post Tx survival (13% versus 14%, p = 0.832), 1-year survival (19% versus 20%, p = 0.855), 3-year survival

Table 2
Renal outcome and patient survival.

No. of patients	226
Stay at ICU (days)	8 (4-21)
Survival:	
90-day survivors, n (%)	195/226 (86)
1-year survivors, n (%)	181/226 (80)
3-year survivors, n (%)	170/226 (75)
5-year survivors, n (%)	92/152* (61)
Renal outcome:	
Follow-up period (days)	1491 (887-2085)
CKD stage at last follow-up:	
CKD 1-3, n (%)	163 (72)
CKD 4, n (%)	15 (7)
CKD 5, n (%)	48 (21)

ICU, intensive care unit; Data is shown as absolute number and percent or median and IQR; *74 individuals were lost to follow-up

(20% versus 27%, p = 0.394) nor 5-year post LT survival (35% versus 41%, p = 0.574). Kaplan Meier plot of 5-year survival according to the alterations of the renal function prior to LT is shown in Fig. 1. Also, improvement of renal function prior to LT did not affect long-term renal function (expressed at CKD stage post LT) (p = 0.8). All patients who underwent kidney transplantation during follow up (n = 5) were at CKD stage 5 prior to LT.

2.3. Stabilization of renal function following terlipressin treatment in patients with HRS prior to LT is not associated with improved post LT patient survival or long-term renal function

50 patients (22%) received terlipressin within 3 months prior to LT for a median duration of 8 days (IQR 4-12 days) as therapeutic agent for treatment of HRS. These patients fulfilled criteria for CKD stage 3 (n = 2, 4%), CKD stage 4 (n = 20, 50%) or CKD stage 5 (n = 28, 56%). In patients with HRS both, MELD score and serum creatinine (peak level within 3 months prior to LT), were significantly higher than in those without (median MELD 31 (IQR 27-37) versus 15 (IQR 11-24), p<0.001; median creatinine 4.4 mg/dl (IQR 3-5.1) versus 1.2 mg/dl (IQR 0.9-2.2), p<0.001). Also, there was a trend towards a higher age of patients with HRS who received terlipressin compared to to those without (median age: 65 years (IQR 54-70) versus 61 years (IQR 53-68); p = 0.053).

Notably, only in 18 of these 50 patients (37%) prolonged stabilization of renal function following terlipressin therapy could be observed (defined as improvement of renal function of at least one CKD stage until time of transplantation). 30 patients (60%), not responding to terlipressin, remained at the same CKD stage, whereas one patient even deteriorated (from CKD stage 4 to 5) despite terlipressin treatment.

Patients with HRS prior to LT had a significantly longer stay on the intensive care unit post LT, with median 19 days (IQR 10-37) versus 6 days (IQR 3-13); p<0.001. Also 90-day, 1-year and 3-year mortality post LT were significantly higher in patients with HRS prior to LT (90-day mortality: 24% versus 11%; p = 0.033; 1-year mortality: 32% versus 17%; p = 0.026; 3-year mortality: 38% versus 21%, p = 0.025). In contrast, 5-year mortality did not differ significantly between patients with and without HRS (46% versus 37%; p = 0.351) pre LT.

Furthermore, stabilization of renal function following terlipressin prior to LT was not associated with a statistically significant improvement of post LT survival in comparison to patients without response (90-day mortality: 22% versus 25%, p = 1; 1-year mortality: 28% versus 34%, p = 0.757; 3-year mortality: 28% versus 44%, p = 0.366; 5-year mortality: 39% versus 50%, p = 0.524). The 1-year survival of patients responding to terlipressin treatment prior to LT is illustrated in Fig. 2.

With regard to the long term follow up of the renal function of surviving patients, those with HRS prior to LT showed significantly higher CKD stages at end of follow-up, in comparison to those without (CKD stage 5: 36% versus 17%; p = 0.026). However, long-term

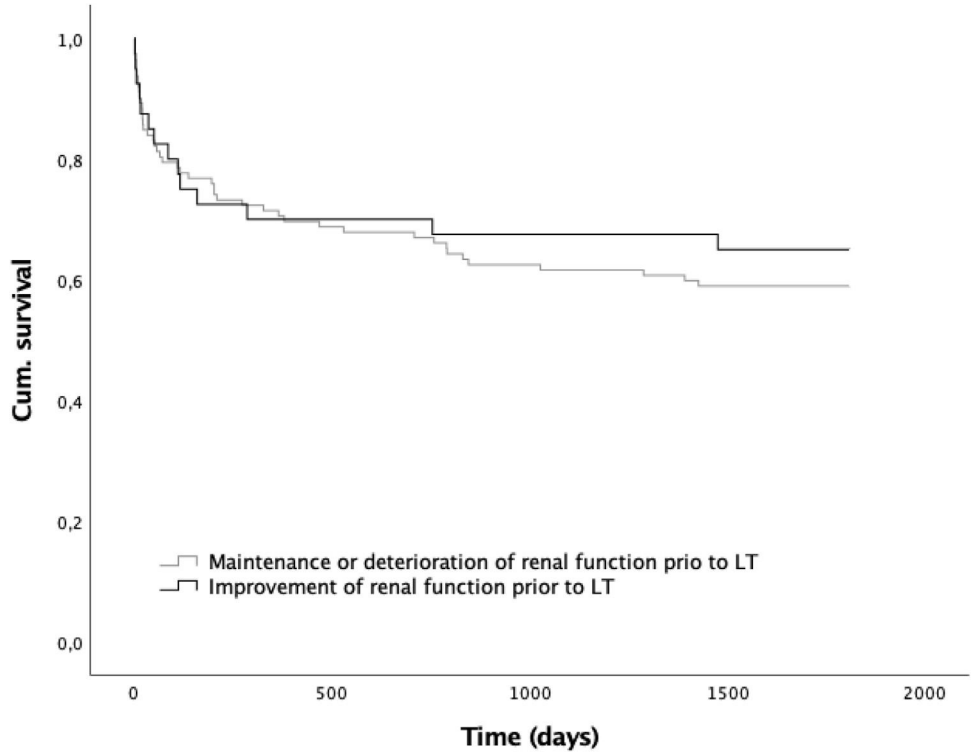

Fig. 1. Kaplan Meier plot of 5-year survival according to alterations of renal function within a time period of 3 months prior to liver transplantation; Log-rank test: p=0.572. (Improvement of renal function: n=64; maintenance or deterioration of renal function: n=162).

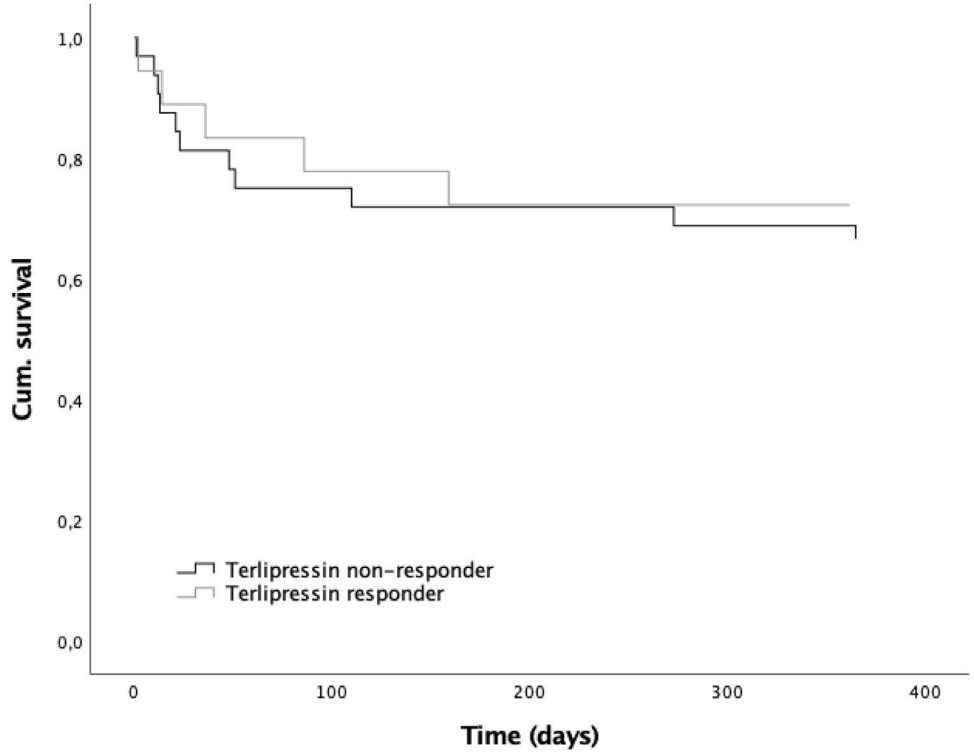

Fig. 2. Kaplan Meier plot of 1-year survival of patients with hepatorenal syndrome responding to terlipressin (n=18) in comparison to patients not responding to terlipressin treatment (n=32) prior to liver transplantation; Log-rank test: p=0.589.

renal outcome (defined as CKD stage at the end of follow up) did not differ significantly between HRS patients who responded to terlipressin therapy prior to LT compared to those who did not (CKD 4: 6% versus 6%, CKD 5: 33% versus 38%, p = 0.484). Furthermore, the GFR levels 5 years post LT did not differ significantly between patients responding to terlipressin prior to LT compared to those who did not respond (median GFR 48 ml/min (IQR 38-59) versus 48 ml/min (IQR 34-65); p = 0.843). The course of renal function (GFR values) in 20 patients that received terlipressin prior to LT surviving 5 years post LT is shown in Fig. 3.

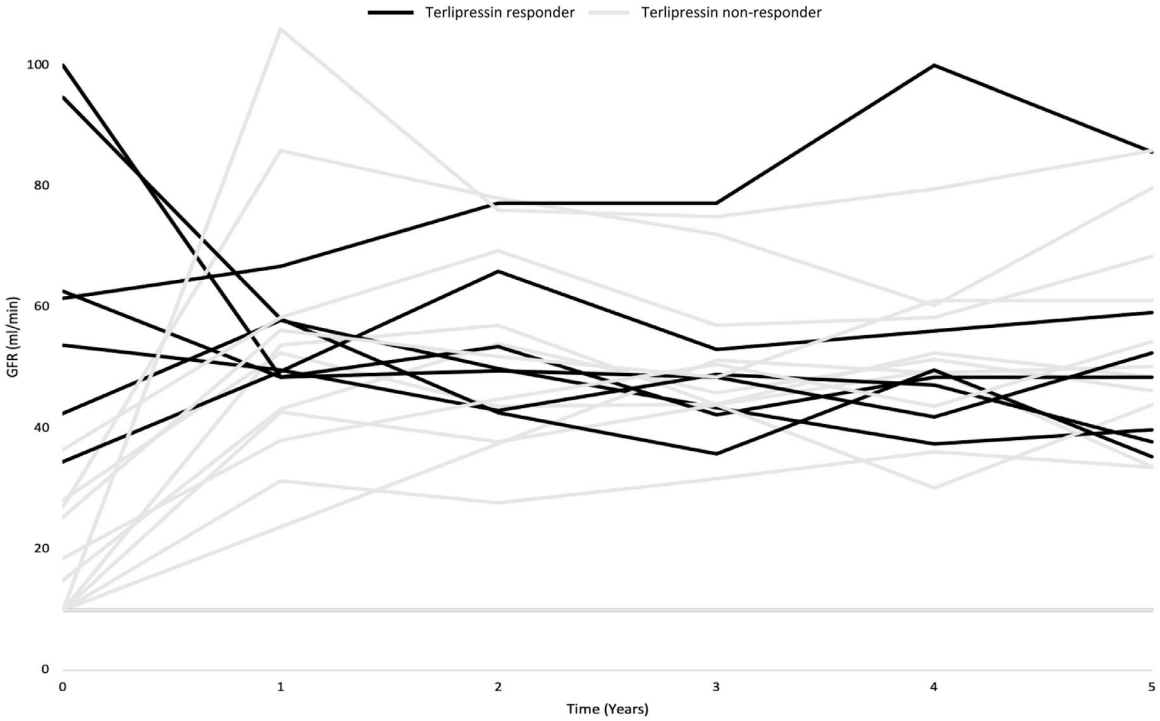

Fig. 3. Course of renal function (GFR values) according to terlipressin response compared to non-response prior to LT in patients surviving 5 years post LT (n=20).

Table 3
Cox hazard regression analysis assessing predictors for reduced 5-year survival.

	HR (95% CI)	*p-value*
Parameters prior to LT:		
Age (years) [#]	1.004 (0.983-1.026)	0.689
Sex	1.589 (0.922-2.783)	0.095
BMI > 30	1.131 (0.573-2.233)	0.723
BMI < 18	1.658 (0.663-4.149)	0.28
MELD > 22[+]	2.389 (1.424-4.009)	0.001
Mechanical ventilation	2.079 (0.945-4.576)	0.069
Vasopressor support	1.22 (0.442-3.364)	0.701
Renal function:		
HRS prior to LT	1.407 (0.817-2.426)	0.218
Response to terlipressin	0.755 (0.272-2.097)	0.59
Creatinine at day of LT[#]	1.283 (1.119-1.471)	<0.001
Nadir Creatinine within 3 months pre LT[#]	1.269 (1.098-1.467)	0.001
Dialysis pre LT	2.111 (1.232-3.614)	0.006
Dialysis post LT	5.142 (2.776-9.524)	<0.001

HR, hazard ratio; CI, confidence interval; BMI, body mass index; LT, liver transplantation
[#] OR per one year or one point increase
[+] optimal MELD cut off according to Youden's index

2.4. Risk factors and impact of dialysis pre and post LT on long-term renal outcome and survival

Forty patients (18%) underwent dialysis at any timepoint within 3 months prior to LT, whereas 35 (16%) were still on dialysis at the day of LT. 99 patients (44%) needed dialysis immediately postoperatively (after LT) or during hospital stay. Median time of necessity of dialysis post LT was 14 days (IQR 5-39 days) in these patients. However, dialysis pre LT did not affect the time on dialysis post LT (p = 0.72). Both, need for dialysis pre LT and post LT were associated with a significant increased 5-year post LT mortality (dialysis pre LT: 59% vs. 34%, log rank: p = 0.005; dialysis post LT: 62% vs. 17%, p<0.001).

2.5. Cox regression analysis for assessment of risk factors for 5-year mortality

Cox hazard regression analysis showed an association of severity of liver disease (MELD) and renal function (both, peak creatinine 3 months prior to LT, as well as serum creatinine at day of LT), dialysis pre and post LT with 5 year post LT survival. Notably, age, BMI (>30 or <18), sex, HRS, response to terlipressin, need for vasopressor therapy or mechanical ventilation immediately prior to LT were not significantly associated with post LT 5-year survival, as shown in table 3.

2.6. Acute-on-chronic liver failure

56 patients out of 146 (38%) fulfilled criteria of ACLF prior to LT. 25 (45%) of these showed improvement/stabilization of ACLF prior to transplantation. At the day of LT 52 patients fulfilled the criteria of ACLF. Severity was classified as ACLF grade 1 (n = 12, 23%), ACLF grade 2 (n = 17, 33%) and ACLF grade 3 (n = 23, 44%). Median time from decompensation to LT was 16 days (IQR 9-40). Presence of ACLF prior to transplantation was associated with significantly higher post transplant mortality rates (90-day mortality: 71% versus 29%, p = 0.001; 1-year mortality: 66% versus 35%, p = 0.001). Improvement of ACLF prior to LT seems to be associated with reduced short-term mortality, however not reaching statistical significance (90-day mortality: 27% versus 73%, p = 0.135; 1-year mortality: 26% versus 74%, p = 0.87).

3. Discussion

Renal dysfunction is a frequent finding among LT recipients and has been shown to be associated with markedly increased post transplant morbidity and mortality [1,13,17]. Particularly, implementation of the MELD score significantly increased the number of patients with renal dysfunction undergoing LT [1,2]. The relevance of a deterioration or an improvement of renal function directly prior to LT is still not fully understood. For example, terlipressin therapy was reported to improve short-term survival in patients with HRS [15]. However, administration of terlipressin in HRS may result in subsequent improvement of serum creatinine, immediate drop of the MELD score and less prioritization on the transplant waiting list. We therefore aimed to evaluate the course of renal function immediately prior to LT and to study its impact on long-term renal outcome and overall survival.

One of the main findings of this study is that improvement of the renal function immediately within 3 month prior to LT, had no significant effect on long-term renal function or overall post LT patient survival (Fig. 1). Looking only at patients with HRS receiving terlipressin, we found that the administration of terlipressin prior to LT was associated with increased 90-day, 1-year and 3-year post LT mortality rates. This is likely due to the fact that patients with HRS had a significantly higher serum creatinine and a higher MELD score than patients without.

We only in 37% of these patients a prolonged stabilization of renal function following to terlipressin therapy, by means of improvement of renal function of at least one CKD stage pre LT, could be observed. Importantly, in our cohort stabilization of renal function following terlipressin did not improve long-term renal function or survival of LT recipients (see Fig. 2): Neither short term survival (90-day mortality) nor long-term survival (at 5-years) differed significantly among these terlipressin responders and non-responders.

Very recently, Piano et al. studied whether treatment with terlipressin and albumin improves post-LT survival. They analysed patients who developed HRS prior to LT being treated with terlipressin (n = 82) and controls without HRS. The authors observed that responders to terlipressin required LT less frequently and had a lower risk of CKD at 1 year after LT. Furthermore, a better 30-day transplant-free survival and a longer LT waiting list time was reported. [18] In contrast, in our study long-term stabilization of the renal function following terlipression therapy was not associated with improved long-tern renal outcome. Notably, whereas Piano and colleagues investigated LT candidates (of which about 70% underwent LT), we exclusively studied patients on the waiting list who then underwent LT. However, in line with Piano et al., we found that stabilization of renal function following terlipressin did not improve post transplant survival.

Our findings are of main importance, as we know that changes of the renal function affect the MELD score and therefore influence the prioritization of organ allocation. We observed that impaired renal function and presence of HRS in particular are strong predictors of increased post LT mortality, much more than necessity of mechanical ventilation or vasopressor support immediately prior to LT. We further observed, that the rate of HRS was clearly higher among patients with suspected or confirmed infection in comparison to patients without infectious complications (68% versus 32%, p<0.001). This shows the great importance and prognostic relevance of bacterial infections among patients with liver disease. Notably, improvement in ACLF before transplantation appeared to be associated with reduced short-term mortality,. However, this finding did not reach statistical significance and should not be overestimated, due to the small number of cases.

Beside this, according to our data, stabilization of renal function following terlipressin administration prior to LT did not result in improved renal or overall outcome in patients with HRS. Beside this,

terlipressin administration and associated alterations of renal function could results in longer waiting times for LT. Therefore, future studies are urgently needed to assess the risk-benefit ratio and definitely clarify the role of terlipressin therapy in liver transplant candidates with HRS.

This study is subject to several limitations. First, as this is a single center observation from a University Hospital in Germany, findings may not be generalizable to other healthcare settings or geographical areas. Second, due to the retrospective manner of the study and the available datasets, KDIGO criteria of AKI, i.e. increase in serum creatinine ≥0.3 mg/dl within 48 h or increase of serum creatinine ≥50% within the prior seven days or reduced urinary output could not be reliably evaluated. However, to our knowledge this is the very first study assessing the impact of changes of renal function directly prior to LT on long-term renal and overall outcome.

4. Conclusions

We observed that poor renal function prior to LT is a strong predictor of worse renal outcome and reduced post LT survival. In particular, nadir GFR levels, as well as necessity of dialysis pre and postoperatively clearly affected survival in this long-term follow up observational study. However, short-term recovery of the renal function, whether related to spontaneous improvement of the renal function, or prolonged stabilization of the kidney function following terlipressin administration in HRS patients, did neither improve long-term renal outcome nor patient survival in LT recipients. Future studies are urgently needed to clarify the role of terlipressin, as therapeutic agent in HRS, and its impact on subsequent alterations of serum creatinine and possible disadvantages the transplant waiting time in LT candidates.

List of abbreviations

LT	liver transplantation
MELD	model for end stage liver disease
SLK	simultaneous liver-kidney transplantation
KALT	kidney-after-liver transplantation
GFR	glomerular filtration rate
HRS	hepatorenal syndrome
CKD	chronic kidney disease stage
IQR	interquartile range

Conflicts of interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Thomas Horvatits: Conceptualization, Formal analysis, Data curation, Writing – original draft. **Peter Hübener:** Data curation. **Marcel Touma:** Data curation. **Karoline Horvatits:** Data curation. **Lutz Fischer:** Writing – review & editing. **Ansgar W. Lohse:** Writing – review & editing. **Martina Sterneck:** Conceptualization, Formal analysis, Data curation, Writing – original draft.

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