Liver transplantation for acute-on-chronic liver failure predicts post-transplant mortality and impaired long-term quality of life

Lukas Goosmann1 | Angela Buchholz2 | Katrin Bangert3 | Valentin Fuhrmann3,4 | Stefan Kluge3 | Ansgar W. Lohse1 | Samuel Huber1 | Lutz Fischer5 | Martina Sterneck1 | Peter Huebener1

1Department of Internal Medicine, I. Medical Clinic and Polyclinic, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2Department of Medical Psychology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
3Department of Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
4Department of Gastroenterology and Hepatology, University Hospital Münster, Münster, Germany
5Department of Visceral Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Correspondence
Dr. Peter Huebener, Department of Internal Medicine, I. Medical Clinic and Polyclinic, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
Email: p.huebener@uke.de

Funding information
Clinician-Scientist Program University Medical Center Hamburg-Eppendorf

Abstract

Background: Among patients with cirrhosis, candidate selection and timing of liver transplantation (LT) remain problematic. Acute-on-chronic liver failure (ACLF) is a severe complication of cirrhosis with excessive short-term mortality rates under conservative therapeutic measures. The role of LT in the management of ACLF is uncertain.

Objective: To assess the impact of ACLF on post-LT survival and long-term graft function, morbidity and quality of life (QoL).

Methods: We retrospectively analysed all cirrhosis patients undergoing LT at our institution between 01/2009 and 12/2014. Median follow-up was 8.7 years. Long-term LT survivors were interviewed with established QoL questionnaires.

Results: Of 250 LT recipients, 98 fulfilled the EASL diagnostic ACLF criteria before LT (‘ACLF-LT’). ACLF associated with reduced post-LT survival (HR for 6-month survival compared to non-ACLF-LT: 0.18; HR for 10-year-survival: 0.47; both \( P < .001 \)) depending on ACLF severity before LT, and mainly inferred by infections both in the early and late phases after LT. In ACLF patients, CLIFc-OFs was superior to MELD score in predicting post-LT mortality. Long-term follow-up revealed comparable graft functions and comorbidity burden in ACLF-LT and non-ACLF-LT survivors. ACLF-LT patients reported significantly impaired health and QoL, particularly with regards to anxiety/depression and physical and psychological health (all \( P < .05 \)). LabMELD score, presence of ACLF at LT and duration of post-LT intensive care associated with poor long-term QoL.

Conclusion: ACLF predicts impaired post-LT survival. While long-term graft function and extrahepatic comorbidities are comparable in ACLF and non-ACLF LT survivors, the strikingly low QoL in many ACLF-LT recipients warrants consideration during follow-up patient care.

KEYWORDS
ACLF, cirrhosis, infection, liver transplantation, quality of life
Advanced chronic liver disease is a substantial global health burden with growing incidence in recent decades. While liver transplantation (LT) has been widely established as a life-saving medical intervention for end-stage acute or chronic liver diseases in many countries, the disparity between organ demand and available donor liver grafts generates complex problems including the selection of suitable transplant candidates, patient prioritization on the waiting list and timing of surgery.

Acute-on-chronic liver failure (ACLF) is a frequent complication of chronic liver disease characterized by single- or multi-organ failure and dismal short-term prognosis. Therapeutic measures aim at the treatment of ACLF triggers as well as medical support of failing organs, yet a high number of patients fails to stabilize under conservative treatment, placing them at high risk of death from progressive multi-organ failure. The role of LT in the management of ACLF patients is a matter of substantial debate. In the ACLF-defining CANONIC and NACSELD studies, only a small minority of patients underwent LT. Subsequent studies yielded conflicting results regarding outcomes of ACLF patients undergoing LT and selection criteria for patients with regard to acceptable post-transplant outcomes are not rigorously studied. We recently reported on the positive impact of clinical stabilization of ACLF patients prior to LT on short-term post-transplant survival. Our findings were generally confirmed in a large patient cohort from the UNOS database, however, effects of pretransplant ACLF on aspects of post-transplant medical care that exceed sheer survival are incompletely understood. Here, we assessed the effects of ACLF on long-term post-transplant survival, graft function, patient morbidity and quality of life (QoL). Our evaluation may aid in the prediction of context-dependent risks and the estimation of realistically attainable goals of LT in the setting of ACLF. Our data further call attention to a strikingly poor QoL in a large fraction of ACLF transplant recipients, necessitating the evaluation of adjunctive measures before and after LT in order to maximize the benefit obtained from each available donor graft.

2 | METHODS

2.1 | Patients

In this retrospective study, we included all adult (age ≥ 18 years at the time of surgery) patients with cirrhosis who underwent their first LT at our institution between January 1st, 2009 and December 31st, 2014. The study was approved by the Aeztsekammer Hamburg (permit no. PV6061). No organs from executed prisoners were used. Data were obtained from electronic medical records including the 3-month pretransplant period. We included the following recipient data: age, gender, age-factored Charlson comorbidity index (CCI), underlying liver disease, presence of hepatocellular carcinoma, hospitalization in an intensive care unit before and after LT, ACLF-relevant organ dysfunction and disease scores (MELD, ACLF grade, CLIFc ACLFs, CLIFc OFs). MELD score was determined via either standard MELD formula (labMELD) or, where applicable, in coordination with Eurotransplant for MELD standard exception points (‘seMELD’). Donor and graft criteria included donor age and BMI, warm and cold ischemia time and the degree of macrovesicular steatosis of the graft liver. For the QoL analysis, we requested via mail all surviving patients to complete a composite survey comprised of EQ-5D-3L, PHQ-4 and WHO-QOL-BREF questionnaires.

2.2 | Diagnostic criteria

Cirrhosis was histologically verified in explanted organs. LT recipients without underlying cirrhosis and re-transplantations were excluded from the study, resulting in 250 patients eligible for analysis. Organ failures and disease scores were determined according to EASL diagnostic criteria. All patients received post-operative antibiotic therapy for 48 hours. Infections in the post-LT phase were diagnosed by (a) clinical, radiological and biochemical evidence for pneumonia, (b) significant bacterial burden in urine culture for urinary tract infection and/or (c) other clinical, radiological or microbiological evidence for infection precipitating anti-infective therapeutic measures. Definitions of multi-drug-resistant gram-negative (MDRGN) pathogens are provided in Appendix S1. Immunosuppression after LT was based on calcineurin inhibitors and corticosteroids. Patients with renal dysfunction received induction therapy with basiliximab and tacrolimus, and HCC patients were routinely switched to tacrolimus/everolimus in the absence of contraindications according to centre protocol. Graft and recipient outcomes were recorded for all patients. Patient follow-up was significantly shorter in ACLF-LT compared to non-ACLF LT recipients as a result of higher early-post-transplant mortality in the former group, but comparable for patients from both groups surviving the 6-month post-transplant phase. All patients underwent standardized scheduled outpatient follow-up including medical history, routine laboratory work and imaging studies.
2.3 | Statistical analysis

Data are presented as median and 25%-75% interquartile range (IQR). Survival curves were compared via Mantel-Cox log-rank test. Metric variables were compared using t-test (two groups) or ANOVA (multiple groups), and dichotomous variables were compared using chi-squared analysis. Survey data were analysed according to the respective manuals\textsuperscript{13-15} including the calculation of sum scores and imputation of missing values. For data management and analyses, we used SPSS 21 (SPSS, Inc, Chicago, IL), GraphPad Prism 8 (Graphpad Software, La Jolla, CA) and Microsoft Excel 2016. All P values reported are two-sided, and P < .05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics are summarized in Table 1. Of 250 cirrhosis patients undergoing LT, 98 patients (39.2%) fulfilled the EASL diagnostic ACLF criteria in the 3-month period preceding transplantation. Of those, 24 patients had ACLF grade 1, 45 patients had ACLF grade 2 and 29 patients had ACLF grade 3. Disease dynamics under conservative therapy effectuated changes in ACLF grade prior to LT as previously described.\textsuperscript{10} Overall, non-ACLF and ACLF transplant recipients did not significantly differ in terms of age, gender, cirrhosis aetiology or comorbidity burden. Hepatocellular carcinoma (HCC) was significantly more prevalent in non-ACLF LT recipients, in whom HCC constituted the indication for LT in almost 50% of patients. At the time of LT, labMELD scores were significantly higher in the ACLF group compared to the non-ACLF group (31.5 points for ACLF vs 12.5 points for non-ACLF patients, P < .0001). Apart from organ functions relevant for MELD score, the prevalence of circulatory, respiratory and/or central nervous system failure was substantially higher in ACLF than in non-ACLF transplant recipients at LT. Liver grafts of transplant recipients did not differ with regard to donor age, donor BMI, graft macrovesicular steatosis or cold and warm ischemia time between groups (Table S1).

3.2 | ACLF prior to LT affects post-transplant mortality

Median follow-up duration was 8.7 (IQR 7.0-9.9) years. The presence of ACLF prior to LT impaired long-term post-transplant patient

| TABLE 1 | Patient characteristics. Data are presented as median (interquartile range) or as a percentage respectively |
|-----------------|-----------------|-----------------|
| Age at LT (years) | 57 (49.25-63) | 57 (50.63-63.25) | \( .18 \) |
| Male gender | 111 (73.0%) | 65 (66.3%) | \( .26^a \) |
| Cirrhosis aetiology | | | |
| Alcohol | 55 (36.2%) | 42 (42.8%) | \( .35^a \) |
| Viral hepatitis | 46 (30.3%) | 23 (23.5%) | \( .25^a \) |
| Other | 51 (33.6%) | 33 (33.7%) | >.99^a |
| Hepatocellular carcinoma | 75 (49.3%) | 12 (12.2%) | <.0001^a |
| Charlson comorbidity index | 6 (5-7) | 6 (5-7) | \( .67 \) |
| ACLF severity at diagnosis | | | |
| ACLF grade 1/2/3 (n) | n/a | 24/45/29 | n/a |
| CLIF-OFs | 12.0 (10.0-15.0) | | |
| CLIFc-ACLFs | 55.5 (48.75-83.0) | | |
| ACLF severity at LT | | | |
| ACLF grade 1/2/3 (n) | n/a | 21/30/38 | n/a |
| CLIF-OFs | 12.0 (9.0-14.0) | | |
| CLIFc-ACLFs | 54 (48.5-64.0) | | |
| labMELD score at LT | 12.5 (9-17) | 31.5 (24-37) | <.0001 |
| Organ failures at LT | | | |
| Liver | 7 (4.6%) | 56 (57.1%) | <.0001^a |
| Kidney | 0 (0.0%) | 90 (91.8%) | <.0001^a |
| Circulation | 1 (0.7%) | 29 (29.6%) | <.0001^a |
| Respiration | 1 (0.7%) | 16 (16.3%) | <.0001^a |
| Coagulation | 2 (1.3%) | 45 (45.9%) | <.0001^a |
| CNS | 39 (39.8%) | | <.0001^a |

Abbreviations: LT, liver transplantation; ACLF, acute-on-chronic liver failure; n/a, not applicable. 
^aFisher’s exact test.
survival, with 48 non-ACLF LT (31.6%) and 50 ACLF-LT recipients (51.02%) passing within the follow-up interval (HR for 10-year-survival in ACLF vs non-ACLF LT recipients: 0.47, \( P < .001 \)) (Figure 1A). Increasing ACLF grade prior to LT correlated with progressively adverse post-transplant prognosis (Figure S1A). Post-transplant mortality of ACLF patients predominantly occurred during the early post-transplant period (HR for 6-month survival in ACLF vs non-ACLF LT recipients: 0.18, \( P < .0001 \)) (Figure S1B), whereas survival was largely indiscernible between survivors of both groups in subsequent months and years (Figure S1C). Of note, patient survival was generally comparable when considering ACLF status at the time of diagnosis or the time of LT (Figure S1D-F). Of all groups, presence of ACLF grade 3 on the day of LT was associated with the poorest post-LT prognosis, compatible with previous findings on the significance of clinical improvement prior to transplant surgery.\(^{10,11}\) When scoring was performed at LT, CLIFc-OFs performed better than labMELD or CLIFc-ACLFs in predicting 180-day post-transplant survival (AUCs for CLIFc-OFs 0.75; for labMELD 0.715; for CLIFc-ACLFs 0.65) (Figure S2A-C and Table S2). Of all scoring systems evaluated, seMELD was least predictive of post-transplant survival, resulting in an AUC of 0.634 (Figure S2D). Within the groups of ACLF- and non-ACLF LT recipients, we observed significant overlap in terms of baseline patient characteristics between short-term and long-term survivors. Among non-ACLF LT recipients, patients with shorter survival tended to be older and had more comorbidities compared to long-term survivors. This association, however, was not observed among ACLF-LT recipients (Table S3).

Lethal recurrence of hepatocellular carcinoma was the leading cause of death in non-ACLF LT recipients, accounting for 15 deaths (10% of patients) (Figure S3A). In contrast, infectious complications accounted for more than two thirds of deaths among ACLF LT recipients, and outnumbered all other causes of death both in the early and late phases after transplantation (Figure 1B). This observation was seemingly independent of initial immunosuppression, consisting of CNI in combination with corticosteroids, to which mTOR inhibitors or mycophenolate mofetil, respectively, were added in the majority of patients from both groups prior to discharge from the hospital. More patients in the non-ACLF group, however, were changed to everolimus-containing immunosuppression after the early post-transplant phase, predominantly to prevent HCC recurrence (Figure S3B-C).

In total, only 10/152 (6.6%) patients from the non-ACLF LT group died from infections, compared to 33 (33.7%) patients in the ACLF-LT group (\( P < .001 \)) (Table S4). Respiratory and (non-biliary) abdominal infections were the most prevalent foci of lethal infections in both groups of patients. Of note, 67 (68.4%) ACLF-LT patients had suffered from infections in the 3-month pretransplant phase, compared to only one (0.7%) patient from the non-ACLF LT group (\( P < .0001 \)). A total of 23 of 33 ACLF-LT patients who died from lethal sepsis had suffered from infections prior to LT, and in 7 (30.4%) of these cases, the same infection focus was identified prior to and after LT, suggesting incomplete resolution of infection prior to LT or re-infection following LT. We were unable, however, to establish a connection between causative pathogens in the pre- and post-transplant phases.

**FIGURE 1** Patient outcomes and causes of death. (A) Kaplan-Meier survival curve for ACLF and non-ACLF LT recipients until 5 years after LT. Number of patients at risk is displayed for time points 0 (day of LT) and 5 years post-LT. (B) Relative frequencies of different causes of death in the respective ACLF and non-ACLF LT cohorts. (C) Suspected or proven sites of lethal infection, and identified pathogens in the respective LT cohorts. MDR = multi-drug-resistant pathogens. MRSA, methicillin-resistant staphylococcus aureus; VRE, vancomycin-resistant enterococci; MDRGN, multidrug-resistant gram-negative bacteria. ***\( P < .001 \)
post-transplant phases (data not shown), partly owing to low positive pathogen culture rates, and partly reflecting a shift of causative pathogens and infection sites following transplant surgery, the initiation of immunosuppression and post-transplant hospitalization, including intensive care. Whenever successfully identified, 60% of pathogens were non-MDR bacteria in both groups, and we detected higher frequencies of 3- and 4-MDRGN bacteria in ACLF LT sepsis decedents despite comparable baseline MDRO prevalence in both groups; this difference, however, did not reach statistical significance because of the low number of lethal infections in the non-ACLF LT cohort (Figure 1C).

### 3.3 Comparable graft functions in ACLF- and non-ACLF LT survivors

We next assessed indicators of liver graft function in ACLF and non-ACLF patients who survived the early phase following LT. Parameters

---

**Figure 2** Liver donor graft and renal function in ACLF and non-ACLF liver transplant recipients. Laboratory values at the indicated time points of follow-up. (B) Results from routine ultrasound examinations of graft livers. (C) APRI score determined at various time points after LT. (D) Renal function stratified by glomerular filtration rate (GFR) at the indicated time points. AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio. *P < .05
of hepatocellular injury (ALT, AST) and liver function (bilirubin, INR) were comparable between both groups throughout the follow-up period (Figure 2A). Chronic rejection occurred in 4 patients from each group (2.6% vs 4.2%, p = n.s., data not shown). Ultrasound examinations yielded abnormal findings with evidence for advanced parenchymal damage in ~25% of liver grafts after 7 years, regardless of pre-LT ACLF status (Figure 2B). On average, the APRI score, a non-invasive index of significant fibrosis with reasonably good diagnostic performance following LT,18,19 did not indicate advanced fibrosis in the vast majority of LT recipients from either group over the entire follow-up period (Figure 2C). Protocol liver biopsies or routine assessments of liver elastometry were not available for the large majority of patients.

Given the very high rates of kidney dysfunction in the ACLF-LT group prior to LT, we assessed indicators of renal function over time in the post-transplant phase. Four patients (4%) from the ACLF-LT group, but no patient (0%) from the non-ACLF LT group underwent combined kidney/liver transplantation. During follow-up, two (1.3%) non-ACLF LT and three (3.1%) ACLF-LT recipients underwent kidney-after-liver transplantation. Chronic kidney disease (CKD) of stage 3 or more (MDRD-calculated GFR < 60 mL/min for >3 months) was present in significantly more ACLF LT recipients after 12 months (P = .03). The prevalence of CKD ≥ grade 3 increased to 73% in the non-ACLF LT group compared to 82% in the ACLF LT group (P = n.s.) after 5 years. End-stage renal insufficiency with haemodialysis was documented only in a small subset of cases (Figure 2D).

## 3.4 ACLF status prior to LT does not affect long-term burden of common post-transplant comorbidities

LT recipients are at considerable risk of extrahepatic morbidity and progressive loss of function of various organ systems.20,21 We thus examined the presence of major metabolic complications over the entire follow-up period. Five years after LT, survivors from both groups had similarly high rates of diabetes mellitus, arterial hypertension, dyslipidemia, obesity and osteoporosis (Table 2). The majority of hypertensive LT survivors developed new-onset hypertension after LT, potentially favoured by CNI therapy. Both non-ACLF and ACLF patients were subject to similar degrees of polypharmacy, with a median of 9 different drugs on a daily basis in both groups. After the initial discharge from the hospital following LT, ACLF transplant recipients were hospitalized for significantly more days in subsequent years (P < .001).

## 3.5 Presence of ACLF prior to LT is associated with significantly impaired long-term quality of life

To better estimate the surviving patients’ perception of their individual outcomes, we conducted a written survey with all LT survivors between 09/2019 and 03/2020 (n = 155 at the time of survey). To this end, we used the EQ-5D-3L, PHQ4 and WHO-QOL-BREF, three well-established health status and QoL questionnaires. The EQ-5D-3L assesses the generic health status in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, the latter being more specifically addressed with the PHQ-4, a four-item screening inventory for anxiety and depression,13,14 The WHO-QOL-BREF allows for cross-cultural comparison of an individual’s QoL, exploring the domains of physical and psychological health, social relationships and environment.15 Overall survey return rate was 58.7% (n = 64 non-ACLF and n = 27 ACLF LT survivors), and comparable between ACLF and non-ACLF LT survivors (Figure 3A). ACLF-LT survey responders were slightly (non-significantly) older than non-ACLF LT responders at LT, otherwise patients were comparable in terms of gender, comorbidity burden and temporal distance to LT, with an expectedly higher prevalence of pretransplant HCC in the non-ACLF LT group (P = .003). In the EQ-5D-3L score, ACLF-LT survivors scored significantly lower on the
unidimensional visual analogue scale regarding their present health status ($P < .05$), with less than half of ACLF-LT patients reaching 70% of their ‘optimal’ health condition (Figure 3B). In the second part of the EQ-5D-3L, patients scored each of the five domains on a three-level scale, from which an index value was normalized to a VAS value set. ACLF LT survivors reached a significantly lower index value ($P = .01$), and particularly reported aggravated problems in the domains of self-care, the ability to perform usual activities and anxiety/depression (Figure 3C). The latter was confirmed in the PHQ-4 score (Figure 3D), where ACLF LT recipients reached significantly higher scores than non-ACLF LT recipients for anxiety and depression (both $P < .05$). The fraction of patients with a domain subscore $\geq 3$, generally serving as a threshold for further psychological evaluation, was more than twice as large among ACLF-LT responders compared to non-ACLF LT responders with respect to both anxiety and depression. In the WHO-QOL-BREF, ACLF-LT survivors scored significantly lower than non-ACLF LT survivors in terms of physical and psychological health, but not in the domains of social relationships.

### Table 1

| Survey responders (% of surviving patients) | non-ACLF LT survivors (n=106) | ACLF LT survivors (n=49) | p value |
|-------------------------------------------|-------------------------------|--------------------------|---------|
| Responder age at LT [years]               | 56 (46.25-61.75)              | 61 (48.65)               | 0.22    |
| Responder male gender [%]                 | 71.9                          | 66.7                     | 0.62    |
| Responder CCI at LT                      | 6 (4-7)                       | 6 (5-7)                  | 0.57    |
| Responder HCC at LT                      | 28 (90.23%)                   | 3 (9.68%)                | **0.003**|
| Time from LT to questionnaire [days]      | 2659 (2166-3327)              | 2731 (2449-3174)         | 0.90    |

**Figure 3** Self-reported health status and quality of life in long-term ACLF- and non-ACLF transplant survivors. (A) Characteristics of survey responders according to their ACLF or non-ACLF pretransplant status. (B) Violin plot of self-reported current state of health on the EQ-5D-3L unidimensional health scale. (C) VAS-indexed and domain-specific states of health of both groups of responders according to EQ-5D-3L questionnaire. (D) Violin plots of cumulative points in the PHQ-4 survey. (E) Violin plots of patients’ self-reported scores in the 4 domains of the WHO-QOL-BREF. CCI, Charlson comorbidity index; HCC, hepatocellular carcinoma. *$P < .05$, **$P < .001$, n.s. statistically non-significant
or patients’ environment (Figure 3E). All results largely correlated with increasing MELD scores when stratifying patients according to labMELD at LT (Figure S4). Importantly, we did not observe pretransplant alcohol use disorder (AUD), a condition frequently associated with psychological comorbidity as a negative predictor of post-LT QoL or anxiety/depression (Table S5), suggesting a minor impact of the aetiology of cirrhosis on post-transplant psychological health. Of particular note, ACLF-LT was not homogenously linked to poor post-LT health and QoL in all patients. Rather, a subset of ACLF-LT patients reached highly satisfactory scores, while the fraction of patients with unsatisfactory self-reported health and QoL was significantly larger among ACLF-LT survey responders. Specifically, 68.9% of non-ACLF LT patients reached a sum score of ≥0.75 on the EQ-5D-3L index, compared to merely 38.5% of ACLF LT responders (P < .05). We thus aimed to identify pre-LT factors associated with impaired QoL. In our analysis, age, gender, comorbidity burden and even the presence of HCC at transplantation were evenly distributed among patients in the highest and the lowest QoL tertile (Table 3). In contrast, the fraction of patients with ACLF prior to LT and the duration of ICU hospitalization following LT were significantly higher in the group with lowest QoL, indicating a significant and measurable impact of pretransplant disease severity and the immediate post-transplant course on long-term well-being of LT survivors.

### TABLE 3 Characteristics of patients from the upper and lower quality-of-life tertile

|                                | Upper 1/3 QoL tertile (n = 31) | Lower 1/3 QoL tertile (n = 31) | P value |
|--------------------------------|---------------------------------|---------------------------------|---------|
| Age at transplantation (years) | 54 (48-62)                      | 59 (48-64)                      | .67     |
| Male gender                    | n = 22 (71.0%)                  | n = 22 (71.0%)                  | >.99a   |
| Cirrhosis aetiology            |                                 |                                 |         |
| Alcohol                        | n = 10 (32.3%)                  | n = 13 (41.9%)                  | .60a    |
| Viral hepatitis                | n = 9 (29.0%)                   | n = 3 (9.7%)                    | .11a    |
| Other                          | n = 12 (39.7%)                  | n = 15 (48.4%)                  | .61a    |
| Hepatocellular carcinoma       | 11 (35.5%)                      | 8 (25.8%)                       | .58a    |
| Charlson comorbidity index     | 6 (4-7)                         | 5 (4-7)                         | .88     |
| index before LT                |                                 |                                 |         |
| MELD score at LT               | 15 (12-21)                      | 19 (10-33)                      | .03     |
| ACLF at LT                     | n = 5 (16.1%)                   | n = 14 (45.2%)                  | .03a    |
| Days between LT and survey     | 2745 (2361-3953)                | 2514 (2043-3930)                | .07     |
| Post-LT ICU hospitalization    | 5 (3-8)                         | 7 (4-21)                        | .03     |
| Post-LT hospitalization        | 23 (17-30)                      | 30 (21-49)                      | .30     |
| WHO-QOL-BREF                   |                                 |                                 |         |
| Domain 1 (physical health)     | 17.71 (17.4-18.86)              | 11.33 (9.14-12.67)              | <.0001  |
| Domain 2 (psychological health)| 17.33 (16.67-18.00)             | 12.80 (11.33-14.20)             | <.0001  |
| Domain 3 (social relationships)| 17.33 (14.67-18.67)             | 12.00 (10.67-13.33)             | <.0001  |
| Domain 4 (environment)         | 19.00 (17.50-19.50)             | 14.50 (13.50-15.50)             | <.0001  |

Abbreviation: ICU, intensive care unit.

aFisher’s exact test.

### DISCUSSION

Establishing clinical and ethical criteria for the allocation of organs for transplantation are a WHO guiding principle and driven by an ever-growing disparity between need and supply of donor liver grafts. Allocation systems are conceptualized in different ways worldwide and largely centred around the aim of preventing wait-list mortality in transplant candidates. Since the MELD score adequately predicts short-term mortality in cirrhosis patients regardless of disease aetiology, it has been widely implemented to prioritize patients within their particular allocation systems. However, several studies have linked high pretransplant MELD scores to adverse post-transplant outcomes, while others have failed to confirm this association (reviewed in Ref. 28), leading to a substantial debate concerning whether and under which circumstances a particular patient should be considered ‘too sick for transplant’, and be removed from the transplant waiting list. Further uncertainties arise from the lack of scope beyond patient and graft survival, and despite the growing academic attention paid to post-transplant quality of life, little is known about potential links between pretransplant disease severity and post-transplant outcomes from the surviving patients’ perspective.

Acute-on-chronic liver failure has recently been characterized as a frequent and severe complication of cirrhosis with high short-term mortality rates. For the majority of ACLF patients, conservative medical therapy alone cannot achieve sufficient and sustained stabilization, and LT has been placed at the centre of therapeutic considerations for these patients with an otherwise dismal prognosis. A large fraction of ACLF patients exhibit contraindications for LT such as severe comorbidities, active alcoholism or ongoing infection. More recent analyses, however, have indicated that in select ACLF patients, LT is feasible with comparably good results, particularly in patients who experience clinical stabilization prior to surgery. Among patients with persistent ACLF grade 3, who are at highest risk of death without LT, the identification of suitable LT candidates remains challenging. In this setting, divergent outcomes have been reported for different cohorts, likely inferred by cohort composition, patient disease dynamics as well as local rules for inclusion and exclusion of LT in participating centres. Thus, the identification of objective and quantifiable predictors of post-LT survival...
in ACLF patients is the unmet goal of an important ongoing scientific debate.

Here, we aimed to investigate multiple dimensions of LT outcome in a large cohort of ACLF and non-ACLF transplant recipients, and extend current knowledge on post-LT dynamics beyond sheer patient survival. We found that ACLF in the pretransplant period predicted short-term post-transplant mortality, with a hazard ratio of 0.18 for 6-month survival in ACLF compared to non-ACLF transplant recipients. Both ACLF grade and MELD score at LT correlated with progressively adverse outcome, in line with previous publications linking particularly very high MELD scores with post-transplant mortality. In our cohort, the pretransplant CLIFc-OFF score, incorporating hepatic encephalopathy, circulatory and respiratory failure in addition to the MELD-relevant parameters bilirubin, creatinine and INR, was superior to MELD score in predicting post-transplant survival, and may be prospectively evaluated to assess its value for clinical decision making. Strikingly, lethal infections constituted the predominant threat to ACLF-LT recipients not only in the first 6 months, but also during the remainder of the follow-up. Similar observations regarding patient survival and infectious complications were recently reported from an UNOS database analysis of >50,000 LT recipients, despite substantial differences between both cohorts in terms of cirrhosis etiology and LT recipient age. The severity of ACLF thus emerges as an important predictor of post-LT complications in suitable transplant candidates, independently of baseline patient characteristics and affiliation to a particular allocation system.

While the majority of ACLF-LT recipients received basiliximab as part of induction therapy caused by impaired kidney function, more non-ACLF LT patients were subsequently switched to everolimus-containing regimes to prevent or delay HCC, thus, immunosuppression may have altered patients’ susceptibility to infection. Significantly more relevant to this phenomenon, however, are likely to be the emerging fields of chronic critical illness and persistent inflammation and immunosuppression, which have been described in sepsis survivors, linked to altered myelopoiesis and reduced effector T-cell functions, and associated with increased mortality for several years following the acute initial event. It seems intuitive that the highly dynamic nature of ACLF, which is frequently complicated by infections, evokes comparable phenomena in patients. In this respect, Monteiro et al have recently linked decompensated cirrhosis to persistent alterations of immune regulation, which may outlast the LT phase and concomitantly affect mechanisms of immune activation, the individual’s response to immunosuppressive therapy and ultimately the risk for serious infections in the post-transplant phase. Our data further suggest that the post-operative course of ACLF-LT, which is frequently characterized by recurrent interventions, repeated rounds of anti-infective therapy and prolonged hospitalization in an ICU environment, favours the emergence of 3- and 4-MRGN pathogens that may ultimately contribute to post-transplant mortality.

Importantly, we did not detect significant differences between ACLF and non-ACLF transplant survivors in terms of graft function, indicating that a large subset of patients from both groups can be successfully transplanted with satisfactory outcomes. Only a small subset of patients underwent combined kidney/liver or kidney-after-liver transplantation. Progressive kidney dysfunction occurred to a similarly high extent in both groups, likely in association with CNI nephrotoxicity, resulting in stage ≥ 3 loss of kidney function in more than 75% of patients after a median of 7 years. Similar observations were made with respect to the dreaded metabolic consequences of LT, including arterial hypertension, diabetes mellitus, dyslipidemia, obesity and osteoporosis, all of which occurred in significantly higher rates in LT recipients from both groups compared to the general population. Thus, ACLF prior to LT affects post-transplant survival and susceptibility to life-threatening infections, but does not impair graft function or infer additional metabolic complications in long-term survivors.

To assess the individual benefit of LT, it is indispensable to take the patients’ perceived QoL into consideration. Besides its potential use as a quality benchmark for LT programmes, this outcome dimension is relevant for physician-patient communication ahead of LT in order to reach truly informed consent. Despite widely comparable graft functions and comorbidities in both groups, ACLF-LT survivors reported a significantly reduced state of health compared to non-ACLF survivors—importantly, all patients were interviewed at home and not during outpatient visits or hospitalization. The VAS-indexed EQ-5D-3L value set of non-ACLF LT recipients (0.874) was largely in line with—even slightly higher than—the reported value for the same-aged German population (0.838). In contrast, ACLF LT recipients scored significantly lower (0.682; \textit{P} = .01), indicating substantially impaired self-reported health, with levels comparable to patients with rheumatoid arthritis, asthma or myocardial infarction. ACF-LT recipients reported more problems in the domains of self-care, their ability to perform usual activities and anxiety/depression. The latter was confirmed in the PHQ-4 score, where more than one in four ACLF LT responders displayed pathologic indicators of anxiety and depression, compared to approximately 12% of non-ACLF LT responders. In the WHO-QOL-BREF, responding ACLF-LT survivors reported impairments of physical and psychological health significantly more often than non-ACLF LT survivors, whereas social relationships and the patients’ environment were evaluated similarly in both groups, indicating a loss of QoL that is independent of current life circumstances, but may rather originate from the (medical) history of the individual patient. Given the high degree of scattering in the QoL results among different LT survivors, we aimed to identify factors that were associated with poor long-term QoL. We found that the presence of ACLF prior to LT, MELD score at LT and length of stay in the ICU following LT were all significantly higher/more prevalent in patients with low long-term QoL, indicating a link between the circumstances of LT and present QoL. Clinical depression was highly prevalent (38.7%) in the lowest QoL tercile (Table S6). Importantly, we did not observe immediate effects of underlying liver disease aetiology on post-LT QoL. Particularly anxiety and depression frequently co-occur with AUD, yet we did not observe differences in long-term QoL between AUD and non-AUD.
The high post-transplant mortality in the ACLF LT group and survey response rates of ~60% of long-term survivors from both groups resulted in a comparably small number of survey responders (n = 64 for non-ACLF-LT and n = 27 for ACLF-LT), which limit the generalizability of our findings. However, our results including significantly impaired self-reported physical and psychological health in ACLF-LT recipients are compatible with the long-term consequences of severe illness, in which post-traumatic stress and physical impairments have been characterized as elements of a post-intensive-care syndrome, and identified as potentially actionable targets in the management of critically ill patients. Our results thus call for further investigations into QoL after ACLF-LT, potentially including detailed pretransplant psychological evaluation and addressing potential roles of structured psychological follow-up in the post-LT phase.

In summary, we have identified ACLF prior to LT as a highly significant predictor of post-transplant mortality, primarily induced by lethal infectious complications, thus mandating rigorous attention from attending physicians to any indication of infection in this highly vulnerable group of patients. While long-term survivors from both groups generally displayed satisfactory graft functions and comparable (high) burdens of metabolic comorbidities, a large group of ACLF patients reported impaired overall health and severe problems in the domains of anxiety and depression. On the other hand, a large fraction of ACLF LT survivors reached QoL levels comparable to non-ACLF LT recipients, indicating a pressing need to identify and address factors which so profoundly affect both post-LT vulnerability as well as the patients' individually perceived gain from transplantation.

ACKNOWLEDGEMENTS
Open Access funding enabled and organized by ProjektDEAL.

CONFLICTS OF INTEREST
All authors declare they have nothing to disclose.

AUTHOR CONTRIBUTIONS
LG—data acquisition, analysis and interpretation, drafting of manuscript. AB—drafting of QoL questionnaire, data analysis and interpretation. KB—critical revision of the manuscript for important intellectual content. VF—critical revision of the manuscript for important intellectual content. SK—critical revision of the manuscript for important intellectual content. AWL—critical revision of the manuscript for important intellectual content. SH—critical revision of the manuscript. LF—critical revision of the manuscript for important intellectual content. SK—critical revision of the manuscript. VF—critical revision of the manuscript for important intellectual content. KB—critical revision of the manuscript for important intellectual content. AB—drafting of QoL questionnaire, data analysis and interpretation of data and drafting of manuscript. All authors approved the final version of the manuscript.

FUNDING INFORMATION
PH is supported by the Clinician Scientist Program of the Faculty of Medicine, University Medical Center Hamburg Eppendorf.

ORCID
Peter Huebener https://orcid.org/0000-0001-7558-7625

REFERENCES
1. Moon AM, Singal AG, Tapper EB. Contemporary epidemiology of chronic liver disease and cirrhosis. Clin Gastroenterol Hepatol. 2020;18(12):2650–2666.
2. Toniutto P, Zanetto A, Ferrarese A, Burra P. Current challenges and future directions for liver transplantation. Liver Int. 2017;37(3):317–327.
3. Arroyo V, Moreau R, Jalan R. Acute-on-chronic liver failure. N Engl J Med. 2020;382(22):2137–2145.
4. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144(7):1426–1437, 1437 e1421–1429.
5. Bajaj JS, O’Leary JG, Reddy KR, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology. 2014;60(1):250–256.
6. Finkenstedt A, Nachbaur K, Zoller H, et al. Acute-on-chronic liver failure: excellent outcomes after liver transplantation but high mortality on the wait list. Liver Transpl. 2013;19(8):879–886.
7. Artru F, Louvet A, Ruiz I, et al. Liver transplantation in the most severely ill cirrhotic patients: a multicenter study in acute-on-chronic liver failure grade 3. J Hepatol. 2017;67(4):708–715.
8. Levesque E, Winter A, Noorah Z, et al. Impact of acute-on-chronic liver failure on 90-day mortality following a first liver transplantation. Liver Int. 2017;37(5):684–693.
9. Artzner T, Michard B, Weiss E, et al. Liver transplantation for critically ill cirrhotic patients: stratifying utility based on pretransplant factors. Am J Transplant. 2020;20(9):2437–2448.
10. Huebener P, Sterneck MR, Bangert K, et al. Stabilization of acute-on-chronic liver failure patients before liver transplantation predicts post-transplant survival. Aliment Pharmacol Ther. 2018;47(11):1502–1510.
11. Sundaram V, Kogachi S, Wong RJ, et al. Effect of the clinical course of acute-on-chronic liver failure prior to liver transplantation on post-transplant survival. J Hepatol. 2020;72(3):481–488.
12. Sundaram V, Mahmud N, Perricone G, et al. Long-term outcomes of patients undergoing liver transplantation for acute-on-chronic liver failure. Liver Transpl. 2020;26(12):1594–1602.
13. Wiesner R, Lake JR, Freeman RB, Gish RG. Model for end-stage liver disease (MELD) exception guidelines. Liver Transpl. 2006;12(12 Suppl 3):S85–S87.
14. Kroenke K, Spitzer RL, Williams JB, Lowe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics. 2009;50(6):613–621.
15. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med. 1998;28(3):551–558.
16. Jalan R, Saliba F, Pavesi M, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol. 2014;61(5):1038–1047.
17. Fernandez J, Prado V, Trebicka J, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol. 2019;70(3):398–411.
18. Pissia A Jr, Borderie D, Bernard D, Scatton O, Calmus Y, Conti F. APRI and FIB-4 scores are useful after liver transplantation independently of etiology. Transplant Proc. 2009;41(2):679–681.
19. Imai H, Kamei H, Onishi Y, et al. Diagnostic usefulness of APRI and FIB-4 for the prediction of liver fibrosis after liver transplantation in patients infected with hepatitis C virus. Transplant Proc. 2018;50(5):1431-1436.

20. Sheiner PA, Magliocca JF, Bodian CA, et al. Long-term medical complications in patients surviving ≥5 years after liver transplant. Transplantation. 2000;69(5):781-789.

21. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl. 2013;19(1):3-26.

22. Claes CGW, Uber A, Graf von der Schulenburg JM. An interview-based comparison of the TTO and VAS values given to EuroQol states of health by the general German population. In: Greiner W, J-MGvdS, Piercy J, editors. EuroQol Plenary Meeting, 1–2 October 1998 Discussion papers Centre for Health Economics and Health Systems Research, University of Hannover, Germany: Uni-Verlag Witte; 1999. p. 13-39.

23. Smith JP, Randall CL. Anxiety and alcohol use disorders: comorbidity and treatment considerations. Alcohol Res. 2012;34(4):414-431.

24. Anker JJ, Kushner MG. Co-occurring alcohol use disorder and anxiety: bridging psychiatric, psychological, and neurobiological perspectives. Alcohol Res. 2019;40(1).

25. Sixty-Third World Health Assembly WHO. WHO guiding principles on human cell, tissue and organ transplantation. Cell Tissue Bank. 2010;11(4):413-419.

26. Trotter JF. Liver transplantation around the world. Curr Opin Organ Transplant. 2017;22(2):123-127.

27. Wiesner RH, McDiarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl. 2001;7(7):567-580.

28. Klein KB, Stafinski TD, Menon D. Predicting survival after liver transplantation based on pre-transplant MELD score: a systematic review of the literature. PLoS One. 2013;8(12):e80661.

29. Lai JC. Defining the threshold for too sick for transplant. Curr Opin Organ Transplant. 2016;21(2):127-132.

30. Gustot T, Fernandez J, Garcia E, et al. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology. 2015;62(1):243-252.

31. Hernaez R, Sola E, Moreau R, Gines P. Acute-on-chronic liver failure: an update. Gut. 2017;66(3):541-553.

32. Jacob M, Copley LP, Lewsey JD, et al. Pretransplant MELD score and post liver transplantation survival in the UK and Ireland. Liver Transpl. 2004;10(7):903-907.

33. Mira JC, Gentile LF, Mathias BJ, et al. Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med. 2017;45(2):253-262.

34. Monteiro S, Grandt J, Uschner FE, et al. Differential inflammasome activation predisposes to acute-on-chronic liver failure in human and experimental cirrhosis with and without previous decompensation. Gut. 2020.

35. van Hout B, Janssen MF, Feng Y-S, et al. Interim scoring for the EQ-SD-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-715.

36. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care. 2003;41(11):1284-1292.

37. Kroenke K, Spitzer RL, Williams JB. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med. 2007;146(5):317-325.

38. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. Crit Care Med. 2010;38(5):1276-1283.

39. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. Crit Care Med. 2011;39(2):371-379.

40. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders’ conference. Crit Care Med. 2012;40(2):502-509.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Goosmann L, Buchholz A, Bangert K, et al. Liver transplantation for acute-on-chronic liver failure predicts post-transplant mortality and impaired long-term quality of life. Liver Int. 2021;41:574–584. https://doi.org/10.1111/liv.14756