Liver, Pancreas and Biliary Tract

Predictive factors for 28-day mortality in acute-on-chronic liver failure patients admitted to the intensive care unit

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ABSTRACT

Background: Acute-on-chronic liver failure (ACLF) is an entity comprising an acute deterioration of liver function in cirrhotic patients, associated with organ failure(s) and high short-term mortality. We aimed to identify predictive factors for short-term mortality in patients admitted with ACLF that may benefit most from liver transplantation.
Methods: Retrospective analysis of patients admitted in ACLF to a tertiary intensive care unit between 2013 and 2017 was performed. The EASL-CLIF acute-on-chronic liver failure in cirrhosis (CANONIC) criteria were used to define ACLF grade. Multivariable analysis using 28-day mortality as an end-point was performed, including severity-of-disease scores and clinical parameters.
Results: Seventy-seven patients were admitted in ACLF over the study period. The commonest aetiology of liver disease was alcohol related 52/77(68%) and the commonest precipitant of ACLF was variceal haemorrhage 38/77(49%). Overall 28-day mortality was 42/77(55%) [ACLF-(grade)1:3/42(7%); ACLF-2:10/42(24%); and, ACLF-3:29/42(69%); $p = 0.002$]. On multivariable analysis MELD ≥ 26 [odds ratio(OR) = 11.559; 95% confidence interval(CI):2.820–47.382; $p = 0.001$], ACLF-3 (OR = 3.287; 95%CI:1.047–10.325; $p = 0.042$) at admission and requirement for renal replacement therapy (OR = 5.348; 95%CI:1.385–20.645; $p = 0.015$) were independently associated with 28-day mortality.
Conclusion: Patients admitted with ACLF to intensive care have a high mortality rate. Defined early thresholds at admission can identify patients at the highest risk that may benefit most from liver transplantation.
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1. Introduction

Acute-on-chronic liver failure (ACLF) is an entity defined by an acute deterioration in liver function in a patient with established chronic liver disease. Generally the condition is precipitated by a super-added acute hepatic injury or an extrahepatic factor which could be treated, and therefore this is a potentially reversible condition [1,2]. Despite this feature, ACLF has a short-term mortality as high as 50–90% [1,3]. Identification of the precipitating factor is crucial for early commencement of specific treatments, which may avoid the development of organ failure(s) and consequent patient death.

The severity of the ACLF episode can be classified according to the chronic liver failure consortium (CLIF-C) sequential organ failure assessment (SOFA) - CLIF-SOFA - score. This classification originated from the chronic liver failure (CLIF) consortium acute in chronic (CANONIC) study and places patients at 3 grades of risk depending on the number of organ failures [1]. Importantly, an increased number of organ failures correlates with an increased 28-day mortality rate. Patients with failure in 1 system (ACLF-1) had a mortality of 23% increasing to around 74% in the case of 3 system organ failure (ACLF-3) [1]. In a previous cohort study of 388 patients admitted with ACLF, reported by Gustot et al. 49.2% improved fol-

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lowing admission whereas 30.4% had a fluctuating disease course while a further 20.4% deteriorated in clinical condition [4]. However, subgroup analysis according to disease severity showed that these rates varied; for ACLF-1 patients 54.5% developed resolution of the episode whereas only 16% of those in the ACLF-3 group recovered [4].

Liver transplantation (LT) is a life-saving procedure considered in some studies mainly for ACLF-3 patients [1,4]. In the CANONIC study patients with more than two organ failures that received a LT had a mortality rate of 20% in comparison with more than 80% for patients that did not undergo LT [1]. Nevertheless, it is still not understood when the optimal time for the assessment of the patients is, what the indication for the procedure should be and which patients would benefit most from it. A detailed discussion about unresolved issues regarding LT for ACLF patients can be found in a recent review article [5]. The early identification of predictive factors for an inferior prognosis and a fatal outcome within an appropriate narrow window of opportunity could potentially select patients for LT before irreversible multiple organ failure and progression of ACLF grade occurs. Currently in the United Kingdom (UK) there is no formal consideration of LT in patients with ACLF, although anecdotally individual centres may have offered LT for selected patients with an acute deterioration of liver function. It is possible that the growing evidence base to support LT in ACLF setting, in conjunction with careful identification and patient selection, could provide hope for some patients with ACLF. Therefore, the aim of this study was to identify independent early predictors for 28-day mortality rate in patients admitted with ACLF to the intensive care unit (ICU) and define possible thresholds where LT most likely becomes a life-saving treatment option to be considered.

2. Patients and methods

2.1. Study design

A retrospective analysis of the outcomes of patients with a diagnosis of ACLF admitted to the Queen Elizabeth Hospital Birmingham liver intensive care unit between January 2013 and December 2017. The diagnosis of ACLF was made based on pre-defined criteria [6] and its severity graded according to the CLIF-SOFA score [1]. The 28-day mortality rate was analysed for the entire cohort and stratified according to episode severity. Predictive factors using 28-day mortality as an endpoint were identified and suggested as possible thresholds for unrecoverable ACLF episodes.

2.2. Study population

The records of admission diagnoses to the ICU over the period of study were screened for the presence of liver diseases. Patients that had a liver related cause for admission were collated with the medical records to ascertain the degree of chronic liver disease and the presence of diagnostic criteria for ACLF as described below.

2.3. Identification of ACLF

The diagnosis of ACLF was based on the European and American Associations for the Study of Liver Disease, as an "acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure" [6]. The severity of the ACLF episode was classified according to the CLIF-SOFA score based on the number of organ failures [1]. The CLIF-SOFA scores 6 components (liver, kidneys, brain, coagulation, circulation and lungs) from 0 to 4, rising accordingly to more severe organ impairment [1]. Parameters to define organ failures and the definition of ACLF grades are described in the Supplementary Tables S1 and S2, in

accordance with the CANONIC study. Septic shock was defined as the occurrence of acute organ dysfunction secondary to documented or suspected infection and in the presence of hypotension not reversed with fluid resuscitation [7].

2.4. Data collection

Demographic data (age, sex, body mass index [BMI], presence of type 2 diabetes mellitus, sarcopenia and other comorbidities, aetiology of the liver disease) was retrieved for analysis. Sarcopenia was assessed by a liver specialist dietician using anthropometry (hand grip, mid-arm muscle circumference, triceps skin-fold thickness) and calculated target body weight for height/age. If the patient was unable to perform a hand grip, a subjective assessment was made by the bedside by two clinicians. Laboratory data at ICU admission and after 48–72 h were recorded to assess the severity of liver disease: platelet count, C-reactive protein (CRP), white cell count (WCC), albumin levels, international normalized ratio (INR), creatinine, bilirubin, and serum sodium levels. The length of ICU and hospital stay, the number and type of organ failures, the primary reason for admission, 28-day, 90-day, and 1-year mortality rates were also recorded. Prognostic score indices for the severity of liver disease (Model for End-Stage Liver Disease [MELD] [8,9] and United Kingdom Model for End-Stage Liver Disease [UKELD] [10]) and for the severity of the acute deterioration (Acute Physiology and Chronic Health Evaluation II [APACHE II] [11] were calculated.

2.5. Statistical analysis

Categorical variables were described and analysed using absolute number and frequency (percentage) and compared using Pearson's chi-squared test or Fisher's exact test. Continuous variables were described using median (interquartile range) or mean (standard deviation) depending on distribution (assessed by the Shapiro–Wilk test) and analysed using Student's t-test for parametric and Mann–Whitney U Test for non-parametric variables. Variables with a p-value less than 0.20 were entered into multivariable analysis model to identify independent predictors of 28-day survival. Multivariable analysis was conducted using a binary logistical regression model, with stepwise backward elimination of variables. Survival was estimated using Kaplan–Meier plots with log–rank tests for differences. Prior to the multivariable analysis, significant continuous variables were dichotomised to increase the practical applicability of our data. The Youden's index was defined from the receiving operating characteristic (ROC) curve analysis in an attempt to identify optimal cutoff values for dichotomisation. However, this did not find any cutoffs that were clearly superior, hence the median values were used. To prevent a biased regression coefficient as a result of data-driven cutoffs values based on information from the entire cohort, each factor was also tested as a continuous variable, a process which returned similar results, in the univariable analysis. Collinearity between explanatory survival variables was tested using Cramer's V test and Spearman's rank correlation coefficients, and highly correlated variables were excluded from the analysis to prevent issues with multicollinearity. For all the tests a $p < 0.05$ was considered as statistically significant. Statistical analysis tests were performed using SPSS version 24 software (IBM Corp, Armonk, NY).

3. Results

During the period of study 77 patients were admitted to the ICU fulfilling the criteria of ACLF. Data from more than 95% of patients was available for each individual variable analysed. For the entire cohort, 49/77 (64%) were male, the median age was 51 years (Interquartile range: 43–57), CLIF-SOFA score 12 (10–14),

Table 1

Clinical variables, distribution of cut offs for severity-of-disease scores at admission and organ support requirement for patients admitted to intensive care unit with acute-on-chronic liver failure. Descriptive analysis for the entire cohort and comparison between 28-day mortality groups.

Variable	All patients (n = 77)	28d survivors (n = 35)	28d non-survivors (n = 42)	p value
Age, years	50 (±11)	51 (±12)	50 (±9)	0.891
Body mass index (kg/m^2)	30 (25–35)	28 (24–35)	31 (26–34)	0.160
Female sex [%(n)]	36 (28/77)	43 (15/35)	31 (13/42)	0.280
Diabetes [%(n)]	25 (19/77)	34 (12/35)	17 (7/42)	0.074
Sarcopenia [%(n)]	17 (13/77)	14 (5/35)	19 (8/42)	0.579
Aetiology chronic liver disease				
ALD [%(n)]	57 (44/77)	57 (20/35)	57 (24/42)	
ALD + other [%(n)]	10 (8/77)	23 (8/35)	0 (0/42)	
NASH [%(n)]	9 (7/77)	6 (2/35)	12 (5/42)	0.695
PSC [%(n)]	8 (6/77)	6 (2/35)	10 (4/42)	
PBC [%(n)]	6 (5/77)	9 (3/35)	5 (2/42)	
Others [%(n)]	9 (7/77)	0 (0/35)	17 (7/42)	
Primary reason for admission				
Variceal bleeding [%(n)]	49 (38/77)	63 (22/35)	38 (16/42)	
Septic shock [%(n)]	22 (17/77)	11 (4/35)	31 (13/42)	0.174
Active alcoholism [%(n)]	4 (3/77)	3 (1/35)	5 (2/42)	
Others [%(n)]	25 (19/77)	23 (8/35)	26 (11/42)	
Variceal bleeding on admission [%(n)]	49 (38/77)	63 (22/35)	38 (16/42)	**0.041**
Distribution of cutoffs for severity-of-disease scores at admission				
ACLF grade 3 [%(n)]	51 (39/77)	29 (10/35)	69 (29/42)	**0.001**
CLIF-SOFA > 12 [%(n)]	61 (47/77)	40 (14/35)	79 (33/42)	**0.001**
UKELD > 61 [%(n)]	49 (38/77)	16 (12/35)	34 (26/42)	**0.016**
MELD > 26 [%(n)]	53 (41/77)	29 (10/35)	74 (31/42)	**0.001**
Length of ICU stay (days)	8 (5–14)	9 (4–17)	7 (5–12)	0.570
Length of hospital stay (days)	17 (11–35)	26 (16–46)	14 (10–25)	**0.003**
Survival (days)	18 (8–316)	335 (50–1018)	9 (5–15)	**0.001**
Mechanical ventilation [%(n)]	69 (53/77)	66 (23/35)	71 (30/42)	0.590
Inotropes requirement [%(n)]	58 (45/77)	54 (19/35)	62 (26/42)	0.499
Renal replacement therapy [%(n)]	60 (46/77)	40 (14/35)	76 (32/42)	**0.001**

Continuous variables presented as median (IQR) or mean (±SD) based on the normality of the distribution. Bold p-values are significant at p < 0.05. Abbreviations: 28d — 28-days; ALD — alcoholic liver disease; NASH — non-alcoholic steatohepatitis; PSC — primary sclerosing cholangitis; PBC — primary biliary cirrhosis; ACLF — acute-on-chronic liver failure; CLIF-SOFA — chronic liver failure consortium (CLIF-C) sequential organ failure assessment (SOFA); UKELD — United Kingdom model for end-stage liver disease; MELD — model for end-stage liver disease; ICU — intensive care unit.

MELD 26 (18–32) and UKELD 61 (53–67). Thirty-eight out of 77 patients (49%) had variceal bleeding as the primary reason for the development of ACLF and 17/77 (22%) an infectious event with septic shock (Table 1). No significant association was found between the severity of ACLF and the identifiable precipitating trigger for its development (Table S3). Alcoholic liver disease alone was the most prevalent cause of the background chronic liver disease (68%) (44/77 alcoholic liver disease alone and 8/77 associated with co-existing aetiologies) followed by non-alcoholic steatohepatitis with 9/77 (12%). Nineteen patients (25%) consumed alcohol in the three months preceding the index admission to ICU.

Twelve patients (38%) were active on the transplant waiting list already, from those 4/12 died within 28 days before being transplanted, 5/12 within 1 year and 3 patients were transplanted. One transplanted patient was admitted in ACLF-1, this was stable within the initial 48–72 h of hospitalisation and transplantation was undertaken after 58 days; the other 2 patients were discharged from hospital and transplanted later. From the remaining patients (n = 65), 3 patients were transplanted, 2 within the index admission and 1 later, after discharge. Forty-one out of sixty-five (63%) patients died within 1 year after the index admission (38 within 28 days and 3 within 1 year). Overall, twelve out of seventy-seven (16%) patients had a clinical deterioration over the initial 48–72 h of hospitalisation. From those 3/12 (25%) died within 28 days and 5/12 (42%) died within 90 days.

3.1. Severity of ACLF

At admission over half of patients were classified as ACLF-3 (39/77 [51%]), followed by ACLF-2 (29/77 [38%]). ACLF-1 was the smallest group [9/77 (12%)]. By day 3 of ITU admission, 45/77 (58%) patients were ACLF-3, 20/77 (26%) ACLF-2, 7/77 (9%) ACLF-1. At the same time point (72 h) one ACLF-3 patient had died and only 4/77 (5%) patients had completely recovered from the ACLF episode (one ACLF-3 and three ACLF-2 patients — none were transplanted during index admission). Six out nine (67%) ACLF-1 patients remained in the same ACLF grade along the first 48–72 h of admission, this proportion was similar for ACLF-2 patients 20/29 (69%) and even higher 34/39 (87%) for ACLF-3 patients. Table 2 and Fig. 1 depicts the pattern of evolution of disease parameters along the time course.

3.2. Mortality in ACLF

The overall 28-day mortality rate was 42/77 (55%). Mortality rate increased with severity of the ACLF episode at admission [33% for ACLF-1, 35% ACLF-2 and 74% for ACLF-3; p = 0.003] (Fig. 2). Retrospectively reviewing the trends of mortality, this difference was still significant at 48–72 h of admission and a higher mortality could be predicted based on severity alone [14% ACLF-1, 51% ACLF-2 and 65% ACLF-3; p = 0.039]. Importantly the 28-day mortality rate was not dictated by short-term clinical evolution (48–72 h) as 37/42 (88%) of patients who died had a stable disease course over this 48–72 h period. Median survival (days) decreased according to ACLF severity, being 312 (15–776) days for ACLF-1, 37 (10–540) for ACLF-2 and 12 (6–41) for ACLF-3 (p = 0.032).

Only two variables were statistically significant on the univariable analysis after 48–72 h from admission that were not significant at admission (platelet and white cell counts). In order to enhance the practical applicability of our data as a future adjuvant tool to select patients for LT, we defined cutoffs for significant continuous risk factors for 28-day mortality (Tables 1 and 2) at admission. Cutoffs for CLIF-SOFA score (12 points), MELD (26 points), UKELD (61 points) and ACLF grade (grade 3) were defined based on the median values, as there were not significant superior values by the Youden's

Table 2

Distribution and comparison of laboratory results and severity of disease scores at admission and after 48–72 h, for patients admitted with acute-on-chronic liver failure in the intensive care unit.

Variable	All patients (n = 77)	28d Survivor (n = 35)	28d Non-survivors (n = 42)	p value	All patients (n = 77)	28d Survivors (n = 35)	28d Non-survivors (n = 42)	p value
	At admission				Data after 48–72 h after admission			
ACLF grade*								
No ACLF	n/a				5 (4/77)	11 (4/35)	n/a	n/a
Grade 1 [%(n)]	12 (9/77)	17 (6/35)	7 (3/42)		9 (7/77)	17 (6/35)	2 (1/42)	
Grade 2 [%(n)]	38 (29/77)	54 (19/35)	24 (10/42)	<0.001	26 (20/77)	26 (9/35)	26 (11/42)	0.011
Grade 3 [%(n)]	51 (39/77)	29 (10/35)	69 (29/42)		58 (45/77)	46 (16/35)	69 (29/42)	
Deceased	n/a				1 (1/77)	n/a	1 (1/42)	n/a
CLIF-SOFA score	12 (10–14)	10 (10–12)	13 (12–14)	<0.001	13 (11–15)	11 (10–13)	14 (12–16)	<0.001
Platelet (x10⁹/L)	70 (51–98)	71 (51–111)	66 (48–90)	0.416	61 (±34)	69 (±37)	55 (±31)	0.019
CRP (mg/L)	37 (17–69)	24 (16–59)	48 (21–86)	0.057	48 (29–69)	46 (27–65)	53 (32–76)	0.370
White blood cells (x10⁹/L)	10.5 (6.0–14.8)	9.1 (5.6–13.1)	11.8 (7.3–15.6)	0.067	10.7 (±5.8)	8.3 (±4.0)	12.8 (±6.3)	0.001
Albumin (g/L)	30 (±8)	30 (±8)	31 (±7)	0.863	30 (26–35)	30 (26–34)	31 (27–35)	0.650
INR	1.8 (1.6–2.4)	1.6 (1.4–2)	2.2 (1.7–2.7)	0.001	2.1 (±0.6)	1.8 (±0.5)	2.3 (±0.7)	<0.001
Creatinine (mmol/L)	112 (80–194)	100 (62–135)	140 (94–216)	0.025	99 (72–148)	76 (57–119)	121 (85–176)	0.001
Bilirubin (mg/dL)	123 (52–373)	69 (29–272)	177 (82–406)	0.003	216 (±177)	177 (±176)	254 (±170)	0.010
Sodium (mEq/L)	136 (129–142)	137 (126–142)	135 (129–142)	0.619	139 (136–145)	142 (137–145)	135 (139–143)	0.206
UKELD	61 (53–67)	55 (52–65)	63 (57–68)	0.047	58 (±7)	53 (51–58)	61 (57–63)	0.001
MELD	26 (17–32)	18 (15–29)	28 (23–34)	<0.001	19 (16–25)	19 (16–25)	28 (23–33)	<0.001
APACHE II	20 (16–26)	18 (15–24)	21 (17–27)	0.162				
Encephalopathy** [%(n)]	21 (16/77)	23 (8/35)	19 (8/42)	0.143	64 (49/77)	54 (19/35)	71 (30/42)	0.074

Continuous variables presented as median (IQR) or mean (±SD) based on the normality of the distribution. Bold p-values are significant at p < 0.05. *According to the CLIF-SOFA score. **According to the West Haven Classification. Abbreviations: n/a — not applicable; ACLF — acute-on-chronic liver failure; CLIF-SOFA — chronic liver failure consortium (CLIF-C) sequential organ failure assessment (SOFA); CRP — C-reactive protein; INR — International normalized ratio; UKELD — United Kingdom model for end-stage liver disease; MELD — model for end-stage liver disease.
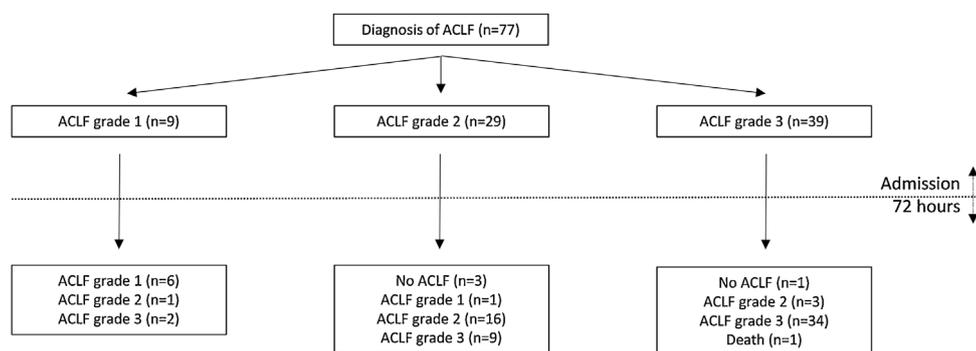

Fig. 1. Flow diagram of progression of grades of acute-on-chronic liver failure (ACLF) patients admitted to the intensive care unit and their outcomes considering the 28-day mortality endpoint.
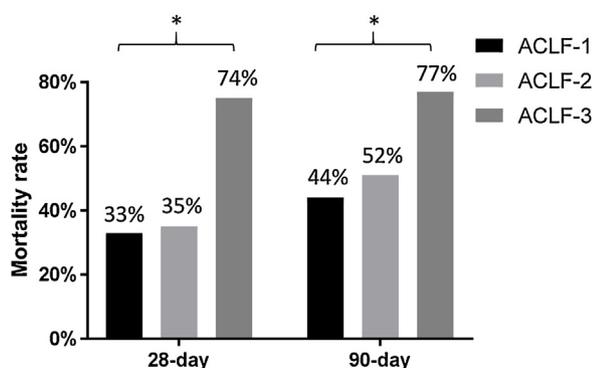

Fig. 2. Short-term and mid-term mortality rates for patients with acute-on-chronic liver failure admitted to the intensive care unit, Queen Elizabeth Hospital, Birmingham, United Kingdom, 2013–2017.

The short-term (28-day) and mid-term (90-day) mortality rates for patients admitted with acute-on-chronic liver failure (ACLF) increased following an increase in the severity of disease as assessed by the ACLF grade score based on the number of organ failure(s). In all panels the bar represents the mortality rate at the time points for each group. Comparison between groups used Pearson's chi-squared test. Statistical significance at *p < 0.05.

index analysis from the ROC curve (data not shown). Requirement for mechanical ventilation and inotropic support were not predictive factors for 28-day mortality on the univariable analysis. However, the need for renal replacement therapy was associated with an increased risk of mortality (p = 0.001). Tables 1 and 2 show the differences between 28-day survivors vs. non-survivors following the index admission (univariable analysis).

3.3. Predictors of mortality

A multivariable logistical regression analysis was performed to identify independent predictors of 28-day mortality following admission on ICU due to ACLF. MELD score and ACLF grade had the defined cutoffs included in the analysis. Due to a highly significant correlation between: (1) CLIF-SOFA and ACLF grade (Spearman's correlation = 0.855); and, (2) UKELD and MELD scores (Spearman's correlation = 0.802); the CLIF-SOFA and UKELD scores were excluded from the multivariable analysis to prevent issues with multicollinearity. Three independent risk factors for 28-day mortality were identified; results are presented in Table 3.

Patients with a MELD score greater than 26 points at admission had a higher short-term mortality rate as represented by the 1-year

Table 3
Multivariable analysis of predictive factors associated with 28-day mortality in patients with acute-on-chronic liver failure.

Variable	Odds ratio (OR)	95% Confidence Interval	p value
MELD ≥ 26	11.559	2.82–47.382	**0.001**
ACLF grade 3	3.287	1.047–10.325	**0.042**
Renal replacement therapy	5.348	1.385–20.645	**0.015**

All factors from Tables 1–3 with p < 0.2 were considered for inclusion in a backward stepwise multivariable model. For severity-of-disease score (MELD, and ACLF grade) cut off values defined by median were used instead of the continuous variables. Body mass index (kg/m²), diabetes mellitus, C-reactive protein (CRP), white blood cells, international normalized ratio (INR), creatinine, bilirubin, APACHE II score were excluded by the stepwise procedure. Bold values are significant at p < 0.05.

Kaplan–Meier survival curve (Log–Rank test $p < 0.001$). A similar figure was seen for ACLF-3 patients (Log–Rank test $p = 0.005$) and the requirement for renal replacement therapy (Log–Rank test $p = 0.022$) (Fig. 3).

4. Discussion

Over the past decade ACLF has gained growing attention from professionals involved in the field of LT. Despite a potential treatable condition, it carries alarmingly high short-term mortality rates [1–3]. LT was shown previously as a potentially successful approach to increase survival rates for a highly selected group of patients [1]. Nevertheless, the correct timing and criteria for LT in this setting is still not defined [5]. This study showed that MELD score greater than 26, ACLF-3 at admission and the requirement for renal replacement therapy were independent predictive factors for 28-day mortality in ACLF patients admitted on ICU. More importantly, those factors were already found to be significant at admission to the ICU and the clinical evolution within the ensuing 48–72 h did not differentiate patients with an inferior outcome once stabilised with established organ support on ICU. This finding is relevant because it shows that these early admission predictive factors could identify patients at the highest risk of death, thereby, offering a small window of time when a select group of patients could be assessed for suitability for LT.

The majority of patients admitted in ACLF to ICU had a severe form of disease requiring multiple organ support. Failure of three or more organs systems was the most prevalent scenario in our cohort and this is likely to be related to the inclusion of patients admitted exclusively to ICU. Short-term mortality rate (28-day) was around 55% and it increased significantly following an increase in the severity of disease at admission. Dynamic changes in the clinical evolution of patients in the first 72 h from admission did not predict overall outcome. Whilst clinical deterioration is still associated with high mortality rates, most patients had a stable course of disease along this period. Conversely, Gustot et al. reported that 49.2% of patients admitted in ACLF improved and that the ACLF grade assessed between days 3–7 was a better predictor of 28-day mortality than at admission [4]. We attribute this difference largely due to variations in cohort composition and the inclusion of patients admitted to ICU only; 51% of our patients ($n = 39$) had ACLF-3 at admission versus 13% at the former study ($n = 50$). In fact, considering only the cohort of ACLF-3 patients in that study, 68% of patients had a stable course of disease [4]. The higher prevalence of most severe forms of disease in our cohort is attributed to the fact that those patients have not been clinically stabilised previously. For these sickest patients, sudden clinical improvements are rare and timely interventions may avoid deterioration and patient death, whereas few patients have (5/77 [6%]) completely recovered or died over these initial 72 h.
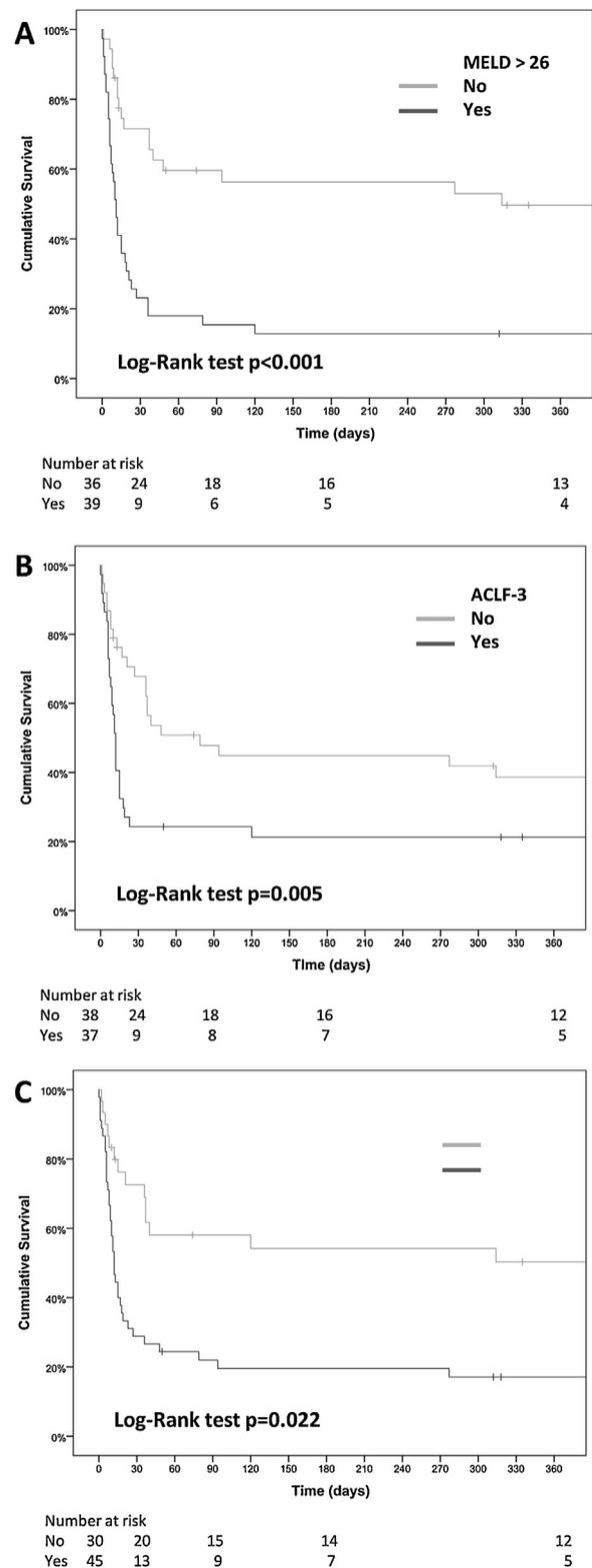
Number at risk
No	36	24	18	16	13
Yes	39	9	6	5	4

Number at risk
No	38	24	18	16	12
Yes	37	9	8	7	5

Number at risk
No	30	20	15	14	12
Yes	45	13	9	7	5

Fig. 3. Kaplan–Meier survival curves for patients with acute-on-chronic liver failure admitted to the intensive care unit, Queen Elizabeth Hospital, Birmingham, United Kingdom, 2013–2017.
The Kaplan–Meier survival curves show the 1-year mortality rate for entire cohort of patients according with the occurrence at admission of a Model for End Stage Liver Disease (MELD) greater than 26 (Graph A), acute-on-chronic liver failure (ACLF) with presence of 3 or more organ failures (ACLF-3) (Graph B) and the requirement for renal replacement therapy (Graph C). The log–rank test was used to compare the differences in survival. A p < 0.05 was considered as statistically significant.

Currently in the United Kingdom there is no clinical guideline defining timings and criteria for listing patients in ACLF for LT. Patient assessment, indication of the procedure and definition of futility is entirely based on the experience of the team. The vast majority of patients in our cohort had not been previously assessed for LT prior to ICU admission and 38/65 (58%) died within 28 days. This raises a need of developing a protocol for the early identification of potential candidates for LT and offering this option whilst they are in the ICU. Our proposal is supported by the CANONIC study [4] where a 1-year survival of 75% was reported in the group that underwent LT in ACLF, including those with ACLF-3 within the first 28-days from the diagnosis. The median time for transplantation was 11 days.

Before the CANONIC study in 2013 there was no consensus for ACLF definition, making comparison with more recent studies difficult. However, in a study involving 175 patients with ACLF (defined as a sudden increase in the MELD score of more than 5 within 4 weeks before transplantation) there were no differences in 3-year survival between ACLF patients and non-ACLF patients that had liver only transplantation [12]. Furthermore living donor liver transplantation using right lobe grafts was reported in a case-series of 32 ACLF patients [13]. Within a follow-up period of 23 months, graft survival was 82% and patient survival 84%, both comparable to rates of non-ACLF patients [13]. Other studies have also successfully used living donor liver transplantation in this context reporting similar survival rates [14,15].

In accordance with our findings, renal dysfunction has been associated with an inferior prognosis for patients with chronic liver disease during an episode of acute deterioration [12,16]. In an analysis of 64 patients admitted to ICU in ACLF, the incidence of renal dysfunction was 58% and was associated with a 28-day mortality rate of 100% [17]. This mortality rate could not be improved with the use of continuous renal replacement therapy [17]. Studies reporting the use of renal replacement therapy in patients with decompensated liver cirrhosis showed that challenges start at the selection of the modality to use (intermittent haemodialysis or continuous renal replacement therapy) [18]. Regarding aetiology, it is speculated that the causes for renal dysfunction in patients in ACLF differ from those in acute decompensations of chronic liver disease and hepatorenal syndrome [3]. It is hypothesised that as inflammation is a fundamental part of ACLF pathogenesis [19] it may play a significant role in renal injury as well as circulatory dysfunction. However, a precise understanding of the importance of different individual components of renal dysfunction in ACLF is still lacking [3]. Despite this, some previous studies exploring the use of anti-inflammatory agents such as N-acetylcysteine [20] and pentoxifylline [21] in patients with hepatorenal syndrome showed a positive impact on renal function. Whether these therapies hold clinical benefit for the renal dysfunction of ACLF remains unclear.

Recently the United Kingdom has adopted a national allocation system that utilises a patient benefit score. This score takes into account both recipient and donor parameters. A hypothetical scenario where an ACLF patient is admitted to ICU with high organ support requirements may yield high patient benefit scores, thereby, increasing the chances of organ allocation to such patients if listed. The identification of patients that are at a high risk of death is fundamental for an early discussion in order to list such patients. UKELD score was a significant predictor of 28-day mortality in our univariable analysis, however it was excluded from the multivariable analysis due to issues with multicollinearity. MELD score and the ACLF grade were both independent predictors of 28-day mortality for patients admitted in ACLF to ICU, those factors having been associated in other studies with a poor prognosis too [1,3,4,22]. On the contrary, patients with an active alcohol history at the time of an acute deterioration or decompensation potentially causes concerns about this patient group when considering LT, whereas other benign and non-self-inflicted aetiologies should perhaps be considered favourably.

Limitations of this study include its retrospective nature and the relatively small number of patients. Despite using a broad screening methodology, we may have lost some cases along the period of study. Moreover, to date, no patient identified at high-risk of 28-day mortality according to our criteria was transplanted. Apart from the identification of the highest-risk patients, other variables are still needing definition for their management, such as the development of a priority system, definition of the best organ supports available and clinical management until transplantation. However, this study provides an initial orientation towards an improvement in the assistance for severely ill patients in ACLF, not only to our service but highlights important points for an area in development. Whilst we have highlighted the importance of early identification of subjects at high risk of short-term mortality, we acknowledge that their individual clinical evolution needs to be taken into consideration during assessment for transplantation.

5. Conclusion

In conclusion, patients admitted in ACLF to ICU showed extremely high mortality rates that increased following a worsening of their clinical condition and liver function. MELD score greater than 26, ACLF grade 3 and requirement of renal replacement therapy were identified as predictive factors for 28-day mortality, and cutoffs were defined for easier clinical identification of patients at high risk of death. Importantly, these factors were as relevant at admission as after short-term clinical follow-up. This finding is crucial in ACLF patients for whom it is likely that a very narrow window of opportunity is available before significant clinical deterioration occurs and futility is considered by treating clinicians. Early identification of patients at the highest risk of such deterioration and where LT is potentially the only life-saving approach is the first step towards an improvement in the management of severely ill ACLF patients.

Conflict of interest

Financial support

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.04.008.

References

[1] 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):1426–37.

[2] Sarin SK, Choudhury A. Acute-on-chronic liver failure. Curr Gastroenterol Rep 2016;18(12):61.

[3] Jalan R, Gines P, Olson JC, et al. Acute-on chronic liver failure. J Hepatol 2012;57(6):1336–48.

[4] 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):243–52.

[5] Choudhary NS, Saraf N, Saigal S, et al. Liver transplantation for acute on chronic liver failure. J Clin Exp Hepatol 2017;7(3):247–52.

[6] Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. Curr Opin Crit Care 2011;17(2):165–9.

[7] Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39(2):165–228.

[8] Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31(4):864–71.

[9] Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124(1): 91–6.

[10] Barber K, Madden S, Allen J, et al. Elective liver transplant list mortality: development of a United Kingdom end-stage liver disease score. Transplantation 2011;92(4):469–76.

[11] Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818–29.

[12] Bahirwani R, Shaked O, Bewtra M, et al. Acute-on-chronic liver failure before liver transplantation: impact on posttransplant outcomes. Transplantation 2011;92(8):952–7.

[13] Liu CL, Fan ST, Lo CM, et al. Live-donor liver transplantation for acute-on-chronic hepatitis B liver failure. Transplantation 2003;76(8):1174–9.

[14] Chok KS, Fung JY, Chan SC, et al. Outcomes of living donor liver transplantation for patients with preoperative type 1 hepatorenal syndrome and acute hepatic decompensation. Liver Transpl 2012;18(7):779–85.

[15] Chen Z, Wen T, Zeng Y, et al. A single institution experience with living donor liver transplantation for acute-on-chronic hepatitis B liver failure. Hepatogastroenterology 2011;58(109):1267–73.

[16] Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology 2008;48(6):2064–77.

[17] Kulkarni S, Sharma M, Rao PN, et al. Acute on chronic liver failure-in-hospital predictors of mortality in ICU. J Clin Exp Hepatol 2018;8(2):144–55.

[18] Gonwa TA, Wadei HM. The challenges of providing renal replacement therapy in decompensated liver cirrhosis. Blood Purif 2012;33(1-3):144–8.

[19] Sen S, Davies NA, Mookerjee RP, et al. Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study. Liver Transpl 2004;10(9):1109–19.

[20] Holt S, Goodier D, Marley R, et al. Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. Lancet 1999;353(9149):294–5.

[21] Akriviadis E, Botla R, Briggs W, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology 2000;119(6):1637–48.

[22] Banares R, Nevens F, Larsen FS, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology 2013;57(3):1153–62.