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Model for end-stage liver disease underestimates mortality of patients with acute-on-chronic liver failure waiting for liver transplantation

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ABSTRACT

Background and Aims: Patients with acute-on-chronic liver failure (ACLF) show excess mortality in MELD-Na based organ allocation for liver transplantation (LT). Whether MELD-based allocation in the Eurotransplant region similarly underprioritizes ACLF patients is unknown.
Methods: 428 patients listed for LT from 01/2010 to 02/2021 at a tertiary center in Germany were screened and 209 patients included as derivation ($n = 123$) and validation cohort ($n = 86$). Competing risk analysis for waitlist mortality and LT as competing events was performed.
Results: 90-day waitlist mortality for patients with MELD $<$ and ≥ 25 at baseline was 9% vs. 33%, respectively ($p = 0.009$). Competing risk analysis shows significantly higher 90-day waitlist mortality in patients listed with ACLF compared to those without ACLF ($p = 0.021$) in the low MELD stratum. Probability of LT was similar between the two groups ($p = 0.91$). In the high MELD group, 90-day waitlist mortality and rates of LT were not significantly different between patients with and without ACLF (31% vs. 20%, $p = 0.55$ and 59% vs. 60%, $p = 0.72$, respectively). Post-transplant survival was similar between patients with and without ACLF. This result was confirmed in the validation cohort.
Conclusion: MELD-based organ allocation in the Eurotransplant region underestimates waitlist mortality in patients with ACLF in lower MELD ranges.

1. Introduction

Cirrhosis is the common end-stage of chronic liver disease. After a compensated stage, acute decompensation may occur and indicate poor prognosis. Recently, acute-on-chronic liver failure (ACLF) was defined as a distinct syndrome, that is characterized by organ failures, significantly increased levels of systemic inflammation and high short-term morbidity and mortality [1–7].

Liver transplantation (LT) is the only curative treatment option for patients in decompensated stages of liver cirrhosis. Organ allocation is performed mostly based on prognostic scores such as MELD or MELD-Na. However, the clinical severity of patients presenting with ACLF seems to be underestimated in different systems of organ allocation, although presence of ACLF pre-transplant does not seem to negatively impact post LT survival [8–10]. Recently, it was shown in a cohort of hospitalized patients with decompensated cirrhosis that 90-day mortality risk for patients with ACLF was higher, compared to the expected death rate based on MELD-Na. However, only 0.8% of the patients with ACLF were considered for LT evaluation and only 0.1% were listed [11]. Moreover, it was recently shown in a North American cohort, that mortality is underestimated in a MELD-Na based organ allocation system in patients listed with ACLF. In particular, patients with ACLF grade 3 in

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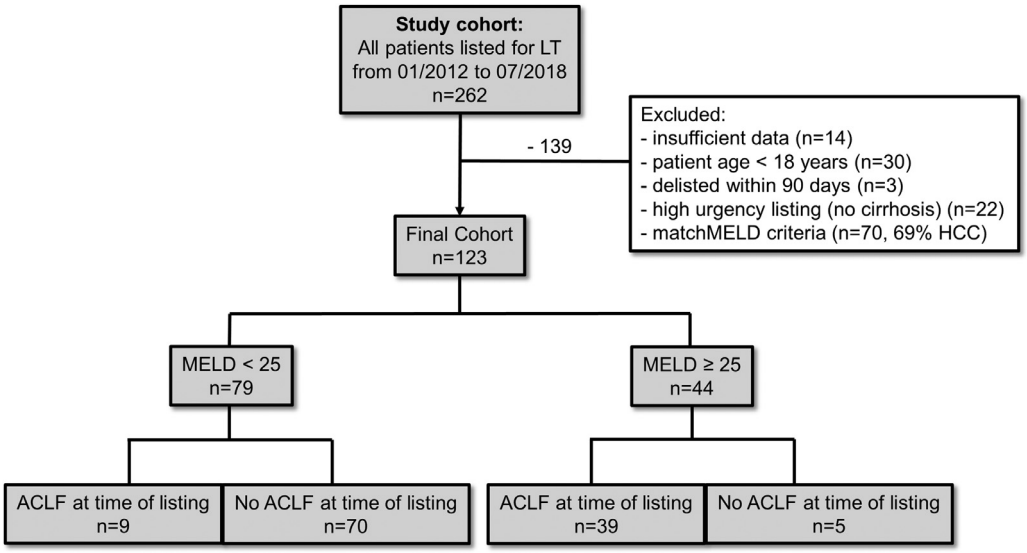

Fig. 1. Flow diagram of inclusion and exclusion of final study cohort ($n = 123$). 262 Patients listed for liver transplantation from 01/2012 to 07/2018 at the University Hospital Bonn were screened. Patients with insufficient data, listed according to the matchMELD criteria (69% of those with HCC), high urgently listed (without underlying cirrhosis), delisted patients and patients below 18 years of age were excluded from the study. A final cohort of $n = 123$ was enrolled stratified by Model for End-stage Liver Disease (MELD) $<$ and ≥ 25 and the presence of acute-on-chronic liver failure (ACLF) at the time of listing.

the low MELD-Na range below 25 points were more likely to die or be removed from waitlist [8].

In some European countries, MELD (rather than MELD-Na) based organ allocation is used for LT, specifically in the countries that are members of Eurotransplant. Whether MELD-based organ allocation underprioritizes ACLF patients similarly to MELD-Na has not been evaluated. Thus, we analyzed data of a MELD based allocation system for LT from our tertiary center in Germany.

2. Methods

2.1. Patients and data collection

All patients that were listed for LT from 01/2012 to 07/2018 at the University Hospital of Bonn were screened ($n = 262$). Patients without sufficient data, patients below 18 years of age and patients that were delisted within 90 days after listing were excluded ($n = 47$). Moreover, patients that were listed according to the matchMELD criteria and those listed for acute liver failure without underlying cirrhosis were also excluded from the study ($n = 92$) (Supplementary Table 1). A cohort of 123 patients was included into the final analysis and stratified to a low MELD (<25) or high MELD (≥ 25) group and further stratified for the presence of ACLF at baseline (Fig. 1). ACLF was graded according to the European Association for the Study of the Liver Chronic Liver Failure Consortium (EASL-CLIF-C) criteria [12]. Baseline was defined as the time of listing for LT. Primary endpoints were waitlist mortality or LT 90 days after listing. An internal validation cohort was recruited by screening additional patients listed for LT from 01/2010 to 12/2011 and from 08/2018 to 02/2021.The same in- and exclusion criteria were applied. After excluding 88 patients, 86 remained eligible for the study (Supplementary Figure 1, Supplementary Table 1). Data was collected on the clinical status at baseline and for the follow up of 90 days after listing. These included standard laboratory parameters, episodes of acute decompensation (AD) and clinical scores (MELD, Child-Turcotte-Pugh (CTP)-Score, CLIF-C-AD Score) as well as survival after LT. The study was performed in accordance with the Helsinki declaration.

2.2. Statistical analysis

Kaplan Meier analysis with log-rank test was performed to evaluate mortality on waitlist with liver transplantation as censoring event stratified by MELD ($<$ and ≥ 25) and the presence of ACLF. Competing risk analysis was performed using the R cmprsk (version 2.2.10) package with death and liver transplantation as competing events, stratified by MELD ($<$ and ≥ 25) and the presence of ACLF to analyze competing endpoints. Univariate and multivariate Cox regression analysis with step-wise forward selection was used to identify predictors of 90-day mortality after listing. Significant parameters in univariate regression analysis and known risk factors (such as age, sex, and cirrhosis etiology) were entered in multivariate regression analyses. Categorical variables are shown as absolutes (percentages) and continuous variables as median (range). Statistical comparisons were performed using the Mann-Whitney-U test for nonparametric variables between 2 unpaired groups, Kruskal-Wallis-H test for nonparametric variables between more than 2 unpaired groups, and Chi-squared test for parametric variables. All statistical analyses were performed in SPSS (version 24.0) and in R software (version 4.0.2), augmented by R Studio (version 1.3.1073).

3. Results

3.1. General characteristics

The primary analysis included 123 patients at time of listing for LT. The patients were predominantly male ($n = 71$, 58%) with a median age of 55 (28–72) years. Etiology of cirrhosis was mostly alcohol-related ($n = 57$, 46%) followed by viral hepatitis B or C ($n = 28$, 23%). Median MELD was 20 (10–40), median CTP-score 9 (5–15) and median CLIF-C AD score 51 (23–83) (Table 1 A)

22 patients (18%) died on waitlist, 36 patients (29%) were transplanted and 65 (53%) were alive at 90 days after listing (Table 1 B). Etiology of cirrhosis was comparable in these groups. Patients undergoing LT presented with the highest median MELD of 31 (14–40), CTP-score of 11 (8–15) and CLIF-C AD score of 60 (44–83) at baseline, compared to patients that died on waitlist. In these two groups, the rate of presence of ACLF at listing was similar (15 (68%)

Table 1A
Baseline characteristics of all patients listed for liver transplantation from 01/2012 until 07/2018.

	Parameters at baseline	All patients (n = 123)
Patient characteristics	Sex (male/female)	71/52 (58/42%)
	Age	55 (28–72)
	BMI	26 (15–43)
	Blood type (A/B/AB/0)	46/23/5/49 (37/19/4/40%)
	Cirrhosis etiology (alcohol/viral/autoimmune/other)	57/28/13/25 (46/23/11/21%)
Scores at listing	MELD	20 (10–40)
	Child-Turcotte-Pugh class (A/B/C)	10/52/61 (8/42/50%)
	CLIF-C AD score	51 (23–83)
	Presence of ACLF	48 (39%)
	ACLF grade (0/1/2/3)	75/22/13/13 (61/18/11/11%)
Medical conditions at listing	Arterial hypertension	22 (18%)
	Coronary artery disease	4 (3%)
	Type 2 diabetes	21 (17%)
Clinical events at listing	Varices	74 (60%)
	Renal replacement therapy	21 (17%)
	Vasopressor use	11 (9%)
	Respiratory failure	9 (7%)
	Ascites	91 (74%)
	HE	39 (32%)
Laboratory at listing	Bilirubin [mg/dl]	4.7 (0.2–39.9)
	Creatinine [mg/dl]	1.1(0.40–5.9)
	INR	1.5 (0.9–3.8)
	Hemoglobin [g/dl]	9.7 (5.6–15.2)
	WBC [G/l]	6.2 (0.9–27.0)
	Thrombocytes [G/l]	68 (15–363)
	Sodium [mmol/l]	138 (111–150)
	CRP [mg/dl]	13.2 (2.2–113.0)
	Albumin [g/l]	29.3 (20.0–49.5)

Table 1B
Baseline characteristics of patients listed for liver transplantation, stratified to patients alive, death and transplanted at 90 days after listing.

	Parameters at baseline	Alive (n = 65)	Death (n = 22)	Transplanted (n = 36)	p
Patient characteristics	Sex (male/female)	38/27 (59/42%)	11/11 (50/50%)	22/14 (61/39%)	0.69
	Age	53 (28–68)	58 (33–66)	57 (39–72)	0.07
	BMI	26 (15/37)	25 (18–43)	27 (17–39)	0.95
	Blood type (A/B/AB/0)	21/16/2/26 (32/35/3/40%)	10/0/0/12 (46/0/0/55%)	15/7/3/11 (42/19/8/31%)	0.09
	Cirrhosis etiology (c2/viral/autoimmune/other)	33/14/8/10 (51/22/12/16%)	8/4/2/8 (36/18/9/37%)	16/10/3/7 (44/28/8/19%)	0.28
Scores at listing	MELD	15 (10–35)	27 (14–40)[$]	31 (14–40)	<0.001
	CTP class (A/B/C)	10/38/17 (15/59/26%)	0/6/16 (0/27/73%)	0/8/28 (0/22/78%)	<0.001
	CLIF-C AD score	47 (23–64)	59 (31–80)[$]	60 (44–83)	<0.001
	Presence of ACLF	9 (14%)	15 (68%)[$]	24 (67%)	<0.001
	ACLF grade (0/1/2/3)	56/7/2/0 (86/11/3/0%)	7/4/5/6 (32/18/23/27%)	12/11/6/7 (33/31/17/19%)	<0.001
Medical conditions at listing	Arterial hypertension	15 (23%)	3 (14%)	4 (11%)	0.27
	Coronary artery disease	2 (3%)	1 (5%)	1 (3%)	0.93
	Type 2 diabetes	12 (19%)	2 (9%)	7 (19%)	0.54
Clinical events at listing	Varices	42 (65%)	9 (41%)	23 (64%)	0.13
	Renal replacement therapy	1 (3%)	6 (27%)	13 (36%)	<0.001
	Vasopressor use	0	5 (23%)	6 (17%)	0.001
	Respiratory failure	0	5 (23%)	4 (11%)	0.001
	Ascites	42 (65%)	18 (82%)	31 (86%)	0.04
	HE	11 (17%)	10 (46%)	18 (50%)	0.001
Laboratory at listing	Bilirubin [mg/dl]	2.6 (0.2–24.9)	12.8 (1.6–34.6)	10.8 (0.4–39.9)	<0.001
	Creatinine [mg/dl]	0.96 (0.40–5.9)	1.4 (0.82–3.43)	1.6 (0.8–5.5)	<0.001
	INR	1.3 (0.9–2.2)	1.6 (1.0–3.5)	1.8 (0.9–3.8)	<0.001
	Hemoglobin [g/dl]	10.6 (5.7–15.2)	8.9 (5.6–14.5)	8.7 (5.9–12.8)	<0.001
	WBC [G/l]	4.9 (0.9–16.1)	8.3 (1.3–21.2)	7.6 (3.2–27.0)	<0.001
	Thrombocytes [G/l]	92 (30–363)	56 (21–328)	55 (15–258)	0.002
	Sodium [mmol/l]	139 (129–150)	136 (120–149)	134 (111–146)	<0.001
	CRP [mg/dl]	8.7 (2.8–57.0)	30.5 (3.3–113.0)	16.3 (2.2–128.0)	<0.001
	Albumin [g/l]	30.7 (20.0–49.5)	28.9 (20.0–45.2)	28.0 (21.1–40.0)	0.20

Abbreviations: ACLF, acute-on-chronic liver failure; BMI, body mass index; CLIF-C AD, CLIF consortium acute decompensation score; CRP, c-reactive protein; CTP, Child-Turcotte-Pugh Score; HE, hepatic encephalopathy; INR, International normalized ratio; LT, liver transplantation; MELD, Model for End-stage Liver Disease; WBC, white blood cells.
*p-values were calculated to compare patients alive not receiving LT vs. patients who died on waitlist vs. patients receiving LT.
$p-values were calculated between patients who died on waitlist vs. patients receiving LT, $ = not significant ($p > 0.05$).

vs. 24 (67%), $p = 0.91$), relevant liver related scores were also not significantly different (MELD: 27 (14–40) vs. 31 (14–40) $p = 0.28$; CTP-score: 10 (7–13) vs. 11 (8–15), $p = 0.34$ and CLIF-C AD score 59 (31–80) vs. 60 (40–83), $p = 0.47$), respectively (Table 1 B). Of patients that neither died nor received LT, only 9 patients (14%) presented with ACLF at listing. Liver related baseline scores (MELD, CTP-Score, CLIF-C AD score) in these 9 patients were significantly lower in comparison to the other groups.

3.2. Evaluation of waitlist mortality stratified by MELD and the presence of ACLF

Patients were stratified in two groups according to 66.7th percentile, which corresponds to a MELD of 25.

The low MELD group (< 25) included 79 (64%) patients, 70 (89%) without ACLF and 9 (11%) with ACLF at the time of listing. The high MELD group (≥ 25) comprised 44 (36%) patients, 5 (11%) without ACLF and 39 (89%) with ACLF (Fig. 1). 90-day mortality for the low MELD group were 9% and 33% ($p = 0.009$) in the no ACLF and ACLF group, respectively (Supplementary Figure 2 A). In the high MELD group, mortality was not significantly different between the groups with and without ACLF (20% vs. 31%, $p = 0.32$) (Supplementary Figure 2 B). ACLF was the most common cause of death in both groups (9 (89%) and 13 (92%), respectively) (Supplementary Table 2).

Univariate analysis for the low MELD (< 25) group showed ACLF grades (1/2/3), bilirubin, hemoglobin, white blood cell count (WBC), and c-reactive protein as significant parameters. A multivariable model including ACLF grades showed a more than 10-fold a 90-day waitlist mortality risk increase for each increase in ACLF grade (HR 10.9 (2.833–42.024); $p = 0.001$). Moreover, bilirubin (HR 1.184 with 95% CI of 1.080–1.298; $p = 0.000$) was an independent predictor for 90-day mortality in the model (Table 2 A).

In the high MELD (≥ 25) group, ACLF grade (1/2/3) was the only independent predictor for 90-day mortality (HR 2.192 with 95% CI of 1.178–4–078, $p = 0.013$) (Table 2 B).

3.3. Competing risk analysis

Additional competing risk analysis was performed with death and LT as competing events. Patients with ACLF in the low MELD (< 25) group showed significantly higher 90-day waitlist mortality after listing compared to patients without ACLF (33% vs. 9%, $p = 0.021$, Fig. 2A). However, the probability to receive LT within 90 days after listing was similar between the two groups (11% vs. 13%, $p = 0.91$).

In the high MELD (≥ 25) group, mortality of patients with ACLF was not significantly different compared to patients without ACLF (59% vs. 60%, $p = 0.55$). They had similar rates of LT as well (31% vs. 20%, $p = 0.72$, Fig. 2B).

3.3.1. Validation cohort

These results were confirmed by an internal validation cohort, in which patients listed with ACLF had significantly higher 90-day waitlist mortality compared to those without ACLF in the low MELD (< 25) group (6% vs. 40%, $p = 0.007$). The rates of LT were similar between the two groups (18% vs. 13%, $p = 0.67$, Supplementary Figure 3 A). Similar to the derivation cohort, neither mortality nor LT rate differed significantly between the two groups in the high MELD (≥ 25) stratum (Supplementary Figure 3 B).

3.4. ACLF episodes of higher ACLF grades after listing

The development of a high ACLF grade or fatal ACLF episode of was analyzed stratified for the different ACLF grades (1–3) at baseline. Of 22 patients listed with ACLF grade 1 ($n = 22$), 10 patients (46%) developed a high grade (2 and 3) or fatal ACLF episode on waitlist (Supplementary Table 3). 8 patients (36%) had at least one ACLF grade 1 episode and 4 patients (18%) did not present with another ACLF episode after listing and either received LT or are still alive; 25 (52%) were transplanted. 42% of the patients listed with ACLF grades 2 and 3 died on waitlist and 46% were transplanted. Regarding patients listed without ACLF ($n = 75$), 27 (36%) developed an ACLF episode on waitlist. 10 (37%) of those died and 15 (56%) were transplanted. Of the 48 patients listed with ACLF, 16 (33%) died on waitlist and 14 (29%) were transplanted. Patients listed without ACLF developed fatal ACLF at significantly lower rates compared to those with ACLF at listing (17% vs. 33%, $p = 0.041$).

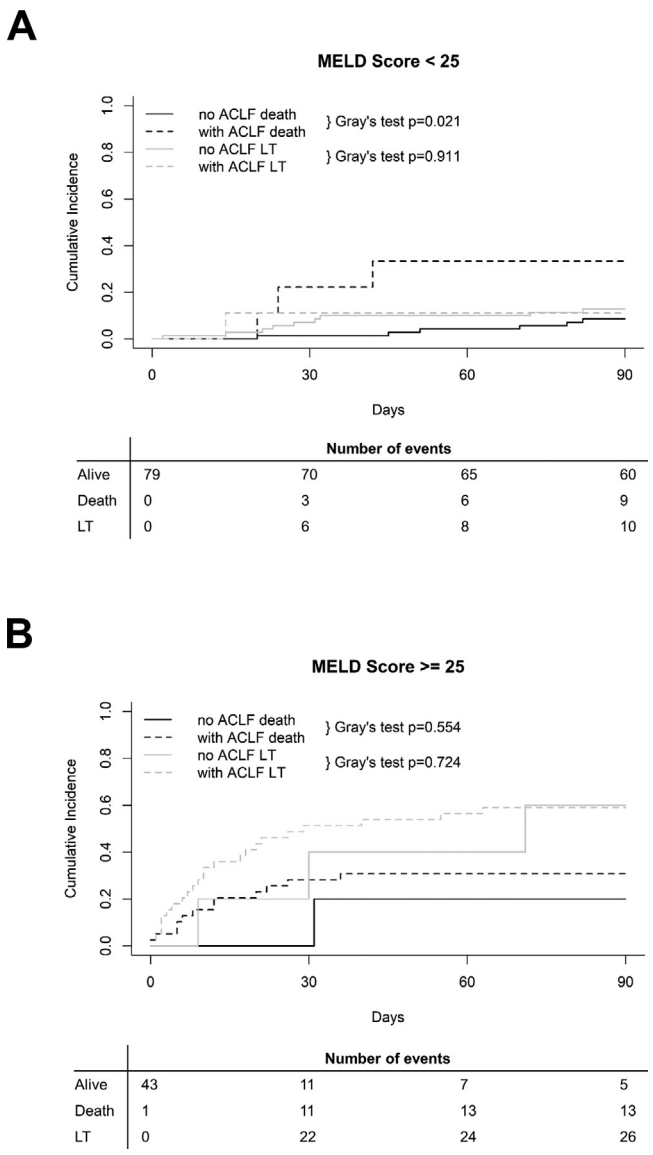

Fig. 2. Competing risk analysis showing mortality and probability of liver transplantation for patients on waitlist with acute-on-chronic liver failure (ACLF) vs. without ACLF in the derivation cohort ($n = 123$). (A) Mortality and probability of liver transplantation calculated according to Gray's test for patients presenting with Model for End-stage Liver Disease (MELD) < 25 at listing. Black line: no ACLF death, dotted black line: with ACLF death, gray line: no ACLF LT (liver transplantation), dotted gray line with ACLF LT. (B) Mortality and probability of liver transplantation calculated according to Gray's test for patients presenting with MELD ≥ 25 at listing. Black line: no ACLF death, dotted black line: with ACLF death, gray line: no ACLF LT, dotted gray line with ACLF LT.

Table 2
Univariate and multivariate Cox regression to identify predictors of 90-day mortality after listing for liver transplantation stratified to patients with MELD < 25 (A) and ≥ 25 (B) at time of listing.

A	Univariate Analysis			Multivariate Analysis		
Parameters	p	HR	95% CI	p	HR	95% CI
Age	0.266	1.045	0.967–1.129	–	–	–
Sex (male/female)	0.540	0.663	0.178–2.469	–	–	–
Etiology (alcohol vs. other)	0.418	0.564	0.141–2.255	–	–	–
Presence of diabetes	0.542	0.524	0.066–4.188			
Presence of varices	0.158	0.388	0.104–1.445			
ACLF grades 1/2/3	**0.002**	**6.024**	**1.911–18.988**	**0.001**	**10.911**	**2.833–42.024**
Circulatory failure	–	–	–			
Mechanical ventilation	–	–	–			
Bilirubin [mg/dl]	**0.001**	**1.121**	**1.064–1.268**	**0.000**	**1.184**	**1.080–1.298**
Creatinine [mg/dl]	0.548	1.218	0.641–2.315			
INR	0.097	6.972	0.705–68.903			
Hb [g/dl]	**0.008**	**0.603**	**0.414–0.879**			
WBC [G/l]	**0.001**	**1.277**	**1.101–1.483**			
Thrombocytes [G/l]	0.870	1.001	0.991–1.010			
Sodium [mmol/l]	0.342	0.933	0.809–1.076			
CRP [mg/dl]	**0.001**	**1.054**	**1.021–1.088**			
Albumin [g/l]	0.797	0.986	0.885–1.098			

B	Univariate Analysis			Multivariate Analysis		
Parameters	p	HR	95% CI	p	HR	95% CI
Age	0.186	1.047	0.978–1.121	–	–	–
Sex (male/female)	0.728	1.125	0.406–3.637	–	–	–
Etiology (alcohol vs. other)	0.875	0.914	0.298–2.803	–	–	–
Presence of diabetes	0.594	0.573	0.074–4.422			
Presence of varices	0.716	0.811	0.263–2.500			
ACLF grades 1/2/3	**0.013**	**2.192**	**1.178–4.078**	**0.013**	**2.192**	**1.178–4.078**
Circulatory failure	**0.044**	**3.456**	**1.031–11.579**	–	–	–
Mechanical ventilation	**0.023**	**4.010**	**1.212–13.262**	–	–	–
Bilirubin [mg/dl]	0.079	1.218	0.641–2.315			
Creatinine [mg/dl]	0.243	0.693	0.374–1.283			
INR	0.177	1.726	0.781–3.815			
Hb [g/dl]	0.494	1.093	0.848–1.408			
WBC [G/l]	0.309	1.052	0.954–1.159			
Thrombocytes [G/l]	0.248	0.994	0.985–1.004			
Sodium [mmol/l]	0.582	1.027	0.934–1.129			
CRP [mg/dl]	0.816	0.999	0.987–1.011			
Albumin [g/l]	0.332	0.956	0.873–1.047			

Abbreviations: ACLF, acute-on-chronic liver failure; CRP, c-reactive protein; Hb, hemoglobin; INR, International normalized ratio; WBC, white blood cells.

3.5. 1-year post-transplant survival

In patients receiving LT, 1-year post-transplant survival was not significantly different between patients listed with ACLF ($n = 24$) and without ACLF ($n = 12$) (71% vs. 83%, $p = 0.37$) (Supplementary Figure 4). Clinical characteristics at baseline of patients listed with ACLF that died or were transplanted stratified to the different ACLF grades at baseline and before death or transplant can be found in the Supplementary material (Supplementary Tables 4 A-C and Supplementary Tables 5 A-C).

4. Discussion

This study shows that patients with low MELD and ACLF have a high 90-day waitlist mortalityand are nevertheless unlikely to receive a liver transplant in a MELD based organ allocation system. Our result indicates underestimation of waitlist mortality in ACLF patients by MELD in the lower score ranges.

ACLF is a distinct syndrome that differs from AD. It is characterized by rapid multiorgan failure, increased signs of systemic inflammation and high short term mortality [1,13]. Elevated circulating levels of inflammatory cytokines in patients with ACLF correlate with the number of organ failures [3]. High short term mortality underlines the need for urgent and aggressive medical treatment for these patients [1,2]. Currently, due to lack of medical options, LT is the only therapy option for many patients with ACLF. However, due to shortness of donor organs, patients with ACLF may be at high risk of waitlist mortality before a suitable organ is available. Recently, in a cohort of hospitalized patients with decompensated cirrhosis 90-day mortality risk was shown to be higher for patients with ACLF compared to the expected death rate based on MELD-Na, which held true also in the subgroups with different ACLF grades [11].

Moreover, in a large North American cohort, mortality in patients with ACLF on waitlist for LT was reported to be underestimated in MELD-Na based organ allocation as these patients display excess mortality on waitlist. Patients with ACLF grade 3 were more likely to die or be removed from waitlist, especially in the low MELD-Na range below 25 [8]. Thus, an underestimation of the clinical severity of patients with ACLF on waitlist for LT has been suggested.

Our data expand the findings for MELD-Na based organ allocation to MELD-based allocation in the Eurotransplant region. This study indicates that patients with ACLF at the time of listing may be similarly underprioritized as they show excess waitlist mortality with a low probability of receiving LT 90 days after listing. Thus, the presence of ACLF when allocating organs needs to be considered in both MELD and MELD-Na based organ allocation systems.

Many patients with ACLF undergo LT, but ACLF specific parameters or scores are not used to allocate donor organs to patients on waitlist, though the prognosis of ACLF is distinct from that of acutely decompensated cirrhosis [1,13,14]. Recent data shows that

despite clear evidence for transplant benefit for patients with ACLF across Europe, wide variations can be found in the practice of waitlisting and LT of patients with ACLF [10]. The CLIF-C ACLF score was developed to fill the gap, because established scores such as MELD or CTP-Score lack parameters of extrahepatic non-renal organ failure and systemic inflammation as ACLF components. This score seems to have greater accuracy in predicting outcomes in patients with ACLF. Thus, the CLIF-C ACLF score may be suitable to derive clinical decisions in the management of patients presenting with ACLF. It has been also discussed that the CLIF-C ACLF score might be useful to identify patients in whom full supportive medical care is futile [2]. MELD or MELD-Na lack parameters assessing extrahepatic non-renal organ failure and systemic inflammation and thus do not fully reflect mortality in ACLF. Therefore, more integrative scores including parameters of ACLF may improve organ allocation for LT.

Moreover, it was shown that patients recovering from ACLF grade 1 have a substantially increased risk of developing a ACLF grade 3 episode later as compared to those who never developed ACLF grade 1 [15]. Our data confirm the high rate of future development of higher ACLF grades or fatal ACLF in case of presence of ACLF grade 1 at listing, which underlines the robustness of our data. Therefore, evaluation and listing for patients with ACLF or past ACLF episodes for LT as a safety net in the event of future deterioration of disease associated with high mortality rates has been discussed [15]. However, LT can only act as a safety net, if ACLF patients are adequately prioritized. However, our data suggests, that this is not the case for the low MELD range.

Considering post-transplant survival, a large North American retrospective study showed that LT improves outcomes in patients with ACLF of all grades [8]. For patients presenting with ACLF grade 3 survival was best when LT was performed within 14 days of listing [8]. It also has been suggested that in certain clinical situations, patients transplanted with ACLF have a higher rate of complications and a lower survival than patients transplanted without ACLF and that the window of LT for patients with ACLF especially in higher grades is rather small [2,9,16]. However, analyses of other cohorts concerning the feasibility of LT in patients with ACLF, indicated comparable post-transplant survival rates to patients without ACLF [17,18]. The CANONIC study showed a survival rate of 80% in the first year of transplanted patients with ACLF especially for patients with a CLIF-C ACLF score < 64 [2]. Another recent European multicenter study with 308 patients listed with ACLF or developing ACLF on waitlist also showed favorable post-transplant survival of 81% [10]. These studies underline the importance of offering LT to ACLF patients. Importantly, the reported high 1-year post-LT survival rates of patients with ACLF are confirmed in our cohort, which supports the concept of LT in ACLF patients.

This study has several limitations. It is a retrospective single center study. However, the presented data is well in line with the current literature and other organ allocation systems, namely MELD-Na for LT. Moreover, analyses of an internal validation cohort confirm our findings. Other confounders such as sarcopenia or frailty at evaluation for LT should be considered, since it has been shown that sarcopenia in patients with liver cirrhosis is related to ACLF development and systemic inflammation [19,20]. This should be explored further but is beyond the scope of this study. More prospective studies for a better selection of ACLF patients suitable for LT are needed, including assessment of suitable timing, setting, number and type of organ failures dependent on different ACLF grades.

In conclusion, our data suggest that clinical severity of patients presenting with ACLF on the waiting list for LT may be underestimated by current MELD based organ allocation, especially in the lower MELD ranges. Modern organ allocation models are needed to adequately prioritize ACLF patients on waiting list.

Conflict of interest

The authors have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.12.011.

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 e9.
[2] Gustot T, Fernandez J, Garcia E, et al. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatol Baltim Md 2015;62(1):243–52.
[3] Clària J, Stauber RE, Coenraad MJ, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. Hepatol Baltim Md 2016;64(4):1249–64.
[4] Trebicka J, Amoros A, Pitarch C, et al. Addressing Profiles of Systemic Inflammation Across the Different Clinical Phenotypes of Acutely Decompensated Cirrhosis. Front Immunol 2019;10:476.
[5] Praktiknjo M, Monteiro S, Grandt J, et al. Cardiodynamic state is associated with systemic inflammation and fatal acute-on-chronic liver failure. Liver Int Off J Int Assoc Study Liver 2020.
[6] 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 gutjnl-2019-320170.
[7] Praktiknjo M, Schierwagen R, Monteiro S, et al. Hepatic inflammasome activation as origin of Interleukin-1α and Interleukin-1β in liver cirrhosis. Gut 2020.
[8] Sundaram V, Jalan R, Wu T, et al. Factors associated with survival of patients with severe acute-on-chronic liver failure before and after liver transplantation. Gastroenterology 2019;156(5):1381–91 e3.
[9] Thuluvath PJ, Thuluvath AJ, Hanish S, Savva Y. Liver transplantation in patients with multiple organ failures: feasibility and outcomes. J Hepatol 2018;69(5):1047–56.
[10] Belli LS, Duvoux C, Artzner T, et al. Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: results of the ELITA/EF-CLIF collaborative study (ECLIS). J Hepatol 2021:S0168827821002610.
[11] Hernaez R, Liu Y, Kramer JR, Rana A, El-Serag HB, Kanwal F. Model for end-stage liver disease-sodium underestimates 90-day mortality risk in patients with acute-on-chronic liver failure. J Hepatol 2020;73(6):1425–33.
[12] Angeli P, Bernardi M, Villanueva C, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406–60.
[13] Trebicka J, Fernandez J, Papp M, et al. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. J Hepatol 2020;73(4):842–54.
[14] Trebicka J, Fernandez J, Papp M, et al. PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis. J Hepatol 2020:S0168827820337727.
[15] Mahmud N, Sundaram V, Kaplan DE, Taddei TH, Goldberg DS. Grade 1 Acute on Chronic Liver Failure Is a Predictor for Subsequent Grade 3 Failure. Hepatology 2020;72(1):230–9.
[16] 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 Off J Int Assoc Study Liver 2017;37(5):684–93.

[17] 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):708–15.
[18] 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 Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc 2013;19(8):879–86.
[19] Praktiknjo M, Clees C, Pigliacelli A, et al. Sarcopenia is associated with development of acute-on-chronic liver failure in decompensated liver cirrhosis receiving transjugular intrahepatic portosystemic shunt. Clin Transl Gastroenterol 2019;10(4):e00025.
[20] Praktiknjo M, Book M, Luetkens J, et al. Fat-free muscle mass in magnetic resonance imaging predicts acute-on-chronic liver failure and survival in decompensated cirrhosis. Hepatology 2018;67(3):1014–26.