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Pre and post-liver transplant outcome of cirrhotic patients with acute on chronic liver failure

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Abstract

Acute on chronic liver failure (ACLF) is a dynamic syndrome, but frequently associated with a high 1 month mortality rate. This is the first study applying the new European Association for the Study of the Liver- chronic liver failure consortium criteria to explore mortality on the waiting list (WL) and early after liver transplantation (LT) in a cohort of Romanian cirrhotic patients that improved or recovered after an episode of ACLF.

To assess frequency and waitlist mortality for different grades of ACLF.

An observational study was conducted; 257 patients with liver cirrhosis included on the WL between 2015 and 2017 were analyzed. The cumulative incidence of waitlist mortality or removal was calculated for combination of competing events using multivariable competing risks regression.

ACLF-1 occurred in 12.07%, ACLF-2 in 7.39% and ACLF-3 in 8.56% of patients. Median Model for End Stage Liver Diseases (MELD) score at the moment of ACLF was 29. The main event while on the WL was death, followed by ACLF; patients with ACLF-3 had a significantly greater subhazard ratio for mortality of 2.25 (1.55–3.26) compared to patients with ACLF-1 or 2. LT proved to be associated with a significantly lower risk of death on the WL at 6 months after inclusion. One and 12 months post-transplant survival of patients with or without ACLF was similar ($P = .77$).

Occurrence of an ACLF episode while on the WL is associated with a significantly high mortality rate, as well as MELD score at inclusion on the WL, renal and liver failure, presence of hepatic encephalopathy. Overall patient short and long term survival after LT is similar to non-ACLF patients in good selected cases.

Abbreviations: ACLF = acute on chronic liver failure, CLIF = chronic liver failure, LT = liver transplantation, WL = waiting list.

Keywords: MELD score, mortality, wait list

1. Introduction

Acute on chronic liver failure (ACLF) occurs in the context of a systemic inflammatory response and is correlated with an increased short-term death rate, depending on the type and number of organ failures. ACLF is a dynamic syndrome different from simple decompensated cirrhosis, may or may not be preceded by detectable triggers and with varying consequences.[1] Overall, ACLF patients are a heterogeneous group. In a prognostic model, chronic liver failure (CLIF)-C organ failure score, age and white cell count were independent predictors of death.[2] The CLIF-C ACLF score measures both hepatic and extrahepatic organ dysfunction and it differentiate much better between survivors and non-survivors compared to Model for End-Stage Liver Diseases (MELD) and the Child-Pugh systems, which underestimate the risk of death in ACLF.

Occurrence of an episode of ACLF might be an indication for liver transplantation (LT). ACLF was identified as the most common cause for transfer to a LT center in New York City but only 9% of the transferred ACLF patients underwent LT.[3] LT can allow the possibility of a definitive treatment and survival benefit in patients with a significant risk of death. Although several studies have shown adequate survival of 70% to 90% at 1 year after LT for ACLF patients, they tend to have longer ICU and hospital stay, as well as increased need for perioperative organ

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support.[4] The MELD, Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation scores have all been recorded to be suitable in predicting mortality in ACLF patients, though their role in predicting the necessity of early LT is not clear.

It is not known what percentage of ACLF patients will recuperate from organ failure and reach a state when they can be electively transplanted. In the study by Gustot et al[5] 35 patients were transplanted within 28 days after ACLF diagnosis. The 1-year likelihood of survival in these patients was 75.3% versus 90% for the 10 patients with ACLF resolution prior to LT.

The aim of our study was to assess frequency of ACLF development on a long waiting list (WL) for LT and to determine waitlist mortality for different grades of ACLF. Secondly, we estimated survival rates after LT in patients with or without ACLF resolution.

2. Material and methods

Diagnostic criteria of ACLF were those described by Moreau et al[6] called "European Association for the Study of the Liver – CLIF Consortium Acute-on-CLF in Cirrhosis (CANONIC). ACLF grade 1 (ACLF-1) at diagnosis was defined by single kidney failure, single non-renal organ failure plus renal dysfunction (creatinine 1.5–1.9 mg/dL) and/or brain dysfunction (grade 1–2 hepatic encephalopathy). ACLF grade 2 (ACLF-2) and ACLF grade 3 (ACLF-3) were defined by the presence of 2 or ≥3 organ failures, respectively. The definitions for organ failures based on the CLIF- Sequential Organ Failure Assessment scale were the following: liver failure - serum bilirubin levels ≥12 mg/dL; kidney failure - serum creatinine levels of ≥2 mg/dL or the use of renal-replacement therapy; cerebral failure - grade III or IV hepatic encephalopathy according to West Haven classification; coagulation failure - an INR ≥2.5 and/or platelet count ≤20 x 10^9/L; circulatory failure - the need of catecholamines or terlipressin support to maintain arterial presssure ≥90mm Hg; respiratory failure - a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (FiO2) of ≤200 or a pulse oximetric saturation (SpO2) to FiO2 ratio of ≤200.

Patients with ACLF were admitted to ICU according to established criteria and artificial liver support systems were used when indicated.

All patients were followed-up prospectively from the inclusion on the WL until death, LT, end of the follow-up period (June 2018). All patients were followed up at least 6 months after inclusion on WL, no matter if they developed or not ACLF while waiting. No patient was transplanted at the ACLF development or while during ICU. Only patients that survived the ACLF episode (with resolution or improvement) were transplanted subsequently electively. Patients that developed an ACLF episode while on the WL were followed until death or waitlist removal from being too sick, LT or June 2018 after discharge from the hospital if they had resolution of ACLF. Resolution was defined by changes from ACLF-3, 2 or 1 to no ACLF. Repeated episodes of ACLF were defined as a new ACLF episode diagnosed according to above mentioned criteria after resolution. Improvement was defined by changes from ACLF-3 to ACLF-2 or 1 and from ACLF-2 to 1. Worsening was defined by changes from ACLF-1 to 2 or 3 and from ACLF-2 to 3.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Fundeni Clinical Institute (No 64769/30.12.2019). Because it is an observational study, performed with a retrospective design using a database and medical records, informed consent was waived by the board. However, all patients signed an informed consent in written form before inclusion on the WL for LT according to our Institute protocol.

2.1. Statistical analysis

Chi-square test, Student t test and nonparametric median test, as well as analysis of variance procedure (ANOVA) were performed for comparisons of categorical and continuous variables, as appropriate. The cumulative incidence of waitlist mortality or removal was calculated for combination of competing events (ACLF or LT), using Fine and Gray multivariable competing risks regression. We also used the competing risks regression to assess the strength of association between different variables and waitlist mortality. For the post-transplant analysis, we compared 1-year survival probability after LT between those with an ACLF episode or without using Kaplan-Meier methods. Survival curves were compared using the log rank test. A 2-tailed P value of $<.05$ was considered statistically significant. Computation was carried out using STATA statistical software release 13.

3. Results

We prospectively included and followed-up 257 patients with liver cirrhosis on the WL for LT in the Center of Gastroenterology and Hepatology of Fundeni Clinical Institute, between January 2015 – December 2017. Main etiology of liver cirrhosis was HBV ± HDV-related (36.5%), followed by HCV (30%) and alcoholic etiology (21%). Hepatocellular carcinoma (HCC) was associated in 22.5% of patients. Table 1 describes the median waiting time on the WL according to our outcomes (ACLF development and/or mortality/removal from the WL). Characteristics of patients that died while on the WL are shown in Table 2.

Table 1

Median time on the WL according to ACLF and/or mortality.

		Time on the WL (d)		
Event on WL	**N**	**Mean (SD)**	**Median (Range)**	**ANOVA (*P*)**
No ACLF, no mortality on WL	170	354.1 (267.7)	260 (1–858)	Time on the WL (ACLF, mortality) $P<.0001$
ACLF and no mortality on WL	29	121.2 (1.4.9)	78 (10–386)	ACLF - $P=.0004$
ACLF and mortality on WL	45	226.2 (204.6)	177 (7–836)	
Mortality, no ACLF on WL	13	254.8 (215.0)	183 (5–612)	$P=.1408$
Total	257	300.5 (253.9)	205 (1–858)	

ACLF = acute on chronic liver failure, WL = waiting list.

Table 2

Characteristics of patients by mortality.

	Alive, N (%)	Deceased, N (%)	Total, N (%)	*P*
Gender				.684
Female	70 (33.6)	15 (30.6)	85 (33.1)	
Male	138 (66.4)	34 (69.4)	172 (66.9)	
ACLF				No vs Yes <.0001
< 0.0001				
No	169 (61.2)	15 (30.6)	184 (71.6)	
Yes	39 (18.8)	34 (69.4)	73 (28.4)	
ACLF-1	24 (11.5)	7 (14.3)	31 (12.1)	No vs grades <.0001
ACLF-2	12 (5.8)	7 (14.3)	19 (7.4)	
ACLF-3	3 (1.4)	19 (38.8)	22 (8.5)	
HCV				.912
No	146 (70.2)	34 (69.4)	180 (70.1)	
Yes	62 (29.8)	15 (30.6)	77 (29.9)	
Ethanol				.149
No	168 (80.8)	35 (71.4)	203 (79)	
Yes	40 (19.2)	14 (28.6)	54 (21)	
HCC				.779
No	160 (77.3)	38 (79.2)	198 (77.6)	
Yes	47 (22.7)	10 (20.8)	57 (22.4)	
Diabetes mellitus				
No	173 (83.6)	35 (72.9)	208 (81.6)	.086
Yes	34 (16.4)	13 (27.1)	47 (18.4)	
Renal insufficiency				< .0001
No	184 (88.9)	20 (41.7)	204 (80)	
Yes	23 (11.1)	28 (58.3)	51 (20)	
Liver insufficiency				< .0001
No	194 (94.2)	33 (68.8)	227 (89.4)	
Yes	12 (5.8)	15 (31.2)	27 (10.6)	
Coagulation insufficiency				< .0001
No	191 (92.3)	24 (50)	215 (84.3)	
Yes	16 (7.7)	24 (50)	40 (15.7)	
Encephalopathy-grade 3–4				<.0001
No	205 (99.1)	32 (66.7)	237 (92.9)	
Yes	2 (0.9)	16 (33.3)	18 (7.1)	
Circulatory insufficiency				<.0001
No	207 (100)	44 (91.7)	251 (98.4)	
Yes	0 (0)	4 (8.3)	4 (1.6)	
Respiratory insufficiency				<.0001
No	207 (100)	40 (83.3)	247 (96.9)	
Yes	0 (0)	8 (16.7)	8 (3.1)	
Upper digestive hemorrhage				.521
No	164 (79.2)	36 (75)	200 (78.4)	
Yes	43 (20.8)	12 (25)	55 (21.6)	
Portal vein thrombosis				.725
No	191 (92.3)	45 (93.7)	236 (92.5)	
Yes	16 (7.7)	3 (6.3)	19 (7.5)	
Spontaneous bacterial peritonitis				<.0001
No	195 (94.2)	34 (70.8)	229 (89.8)	
Yes	12 (5.8)	14 (29.2)	26 (10.2)	
Other infections				<.0001
No	201 (97.1)	29 (60.4)	230 (90.2)	
Yes	6 (2.9)	19 (39.6)	25 (9.8)	
Refractory ascites with repeated paracentesis				<.0001
No	176 (85)	26 (54.2)	202 (79.2)	
Yes	31 (15)	22 (45.8)	53 (20.8)	
MELD score at inclusion on the WL				.001
< 18	161 (77.4)	26 (53.1)	187 (72.8)	
>=18	47 (22.6)	23 (46.9)	70 (27.2)	
MELD score at ACLF				.003
< 29	26 (65)	10 (30.3)	36 (49.3)	
>=29	14 (35)	23 (69.7)	37 (50.7)	
Number of complications				<.0001
0	114 (55.4)	7 (14.6)	121 (47.6)	
1–3	88 (42.7)	20 (41.7)	108 (42.5)	
4–8	4 (1.9)	21 (43.7)	25 (9.9)	

ACLF = acute on chronic liver failure, WL = waiting list.

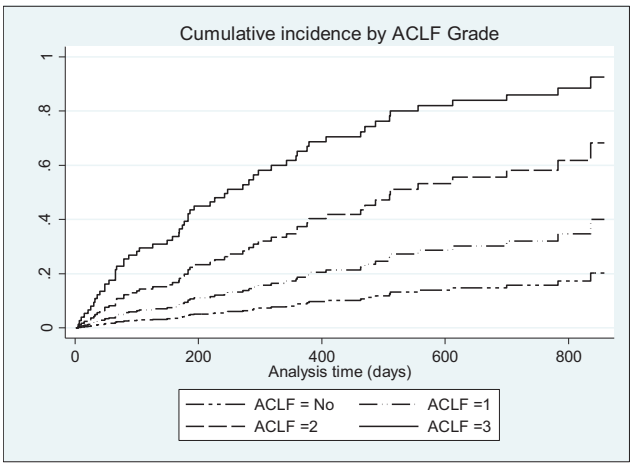

Figure 1. Cumulative incidence of mortality or removal from the WL by ACLF grade. ACLF = acute on chronic liver failure, WL = waiting list.

ACLF-1 occurred in 12.07% (n = 31) of patients, ACLF-2 in 7.39% (n = 19) and ACLF-3 in 8.56% (n = 22). Median MELD at inclusion on WL for patients that developed an ACLF episode while on the WL was significantly higher (19 vs 12, $P < .0001$) compared to patients without ACLF. Median MELD score at the moment of ACLF was 29. Median MELD at inclusion on the WL was significantly higher for patients that were transplanted compared to patients who did not underwent LT (16.5 vs 13, $P = .005$). However, median MELD score for patients with an ACLF episode that were transplanted did not differ compared to patients with ACLF and without LT (27 vs 30, $P = .12$).

Figure 1 shows the cumulative incidence of 1-year mortality after inclusion on the WL among the study cohort. Probability of mortality within 1 year was significantly greater for patients with ACLF-3 than the other groups ($P < .0001$). Figure 2 shows that the highest probability of dying/removing from the list after 1 year was for patients with MELD ≥18 at inclusion on WL and developing an ACLF episode. MELD score at inclusion is significantly associated with occurrence of ACLF (OR = 1.25; 95%CI = 1.17 – 1.33; $P < .0001$). MELD score of 18 at inclusion on the WL had the highest accuracy (78.21%) to predict occurrence of ACLF.

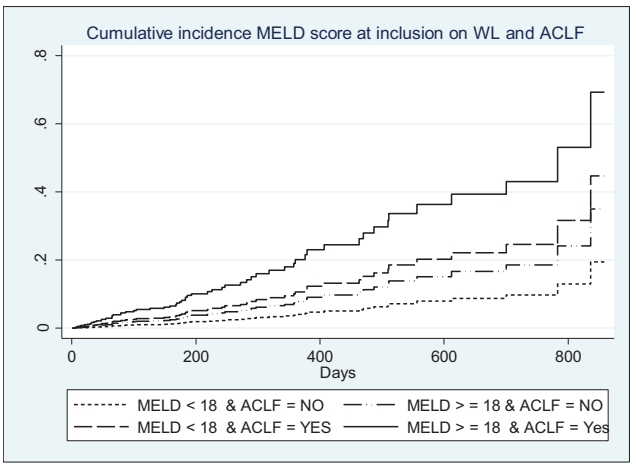

Figure 2. Cumulative incidence of mortality or removal from the WL by MELD score at inclusion on WL and occurrence of ACLF. ACLF = acute on chronic liver failure, WL = waiting list.

Table 3

Sub hazard ratios obtained by multivariate competing-risks regression regarding the removal from the waitlist.

	Estimated sub hazard ratios (SHR) evaluated by competing-risk regression	
Parameter	**SHR (95%IC)**	***P***
ACLF	4.35 (1.88–10.03)	.001
LT	0.10 (0.01–0.85)	.035
Mortality	15.52 (5.80–41.50)	<.0001
Grade ACLF	2.25 (1.55 – 3.26)	<.0001
MELD score at inclusion on the WL	2.98 (1.75 – 5.08)	<.0001
MELD score at first ACLF episode	0.47 (0.24 – 0.92)	.028
Renal insufficiency	2.40 (1.26 – 4.58)	.008
Liver insufficiency	2.43 (1.36 – 4.32)	.003
Encephalopathy-grade 3–4	4.43 (2.57 – 7.64)	<.0001

ACLF = acute on chronic liver failure, CI = confidence interval, LT = liver transplantation, WL = waiting list.

Patients that were transplanted had in a significantly higher proportion an ACLF episode while on the WL, but only ACLF grade 1 or 2 compared to those without LT ($P < .0001$); as well as hepatocellular carcinoma ($P = .007$). Patients with HCV-related cirrhosis were transplanted in a significantly lower proportion compared to patients with other etiologies of cirrhosis ($P = .04$). Also, transplanted patients had in a lower proportion hepatic encephalopathy grade 3 to 4 ($P = .005$) or prior LT infections (excepting spontaneous bacterial peritonitis) ($P = .003$). Patients that underwent LT had a baseline MELD at inclusion ≥18 in a significantly higher proportion (46.05% vs 19.34%, $P < .0001$). 40% of patients developing an ACLF episode are removed from the WL (death) in 6 months if they are not transplanted.

3.1. Risk factors associated with mortality/removal from the WL

Table 3 shows the results of multivariable competing risks regression model, using death or waitlist removal from the WL as the primary outcome and ACLF as the competing event.

In our analysis, we found that the main event while on the WL was death, followed by ACLF. Patients with ACLF-3 had a significantly greater subhazard ratio for mortality of (95%CI) 2.25 (1.55–3.26) compared to those patients with ACLF-1 or 2. Regarding MELD category at inclusion on WL, the higher the score the greater the mortality within 6 months on WL. However, MELD score at first ACLF episode did not yield a greater risk of mortality at 6 months after listing. LT proved to be associated with a significantly lower risk of death on the WL at 6 months after inclusion.

3.2. Overall survival in patients that underwent LT

On the WL, median time from an ACLF episode to LT performance was 4.9 months. Median overall follow-up after LT was 12.6 months. There is no difference regarding post-LT survival in patients with or without ACLF while on the WL (95.5% vs 94.3% at 1 month; 80.1% vs 85.5% at 12 months, log-rank $P = .77$) (Fig. 3).

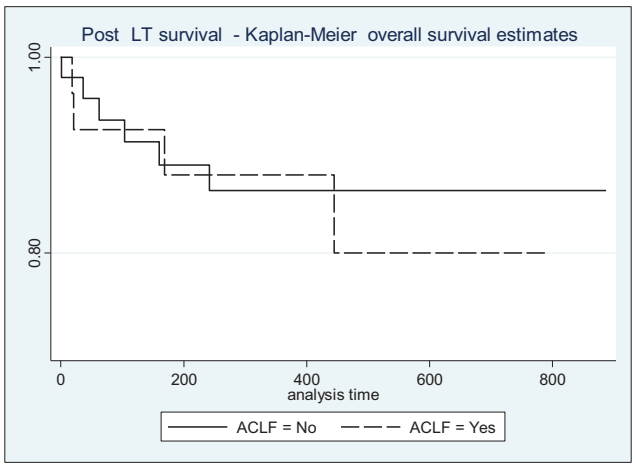

Figure 3. Overall survival in patients that underwent LT in the presence of a previous episode or without an episode of ACLF. ACLF = acute on chronic liver failure, LT = liver transplantation.

4. Discussion

Patients with a MELD score ≤18 represent an important proportion of patients on the transplant waitlist worldwide, as well as in Romania. In USA, 71.9% of 12,487 active LT candidates had a MELD ≤18. Based on the current allocation models these patients have the lowest priority for LT. However, they are still prone to death from complications of liver disease such as infection, bleeding, malignancy, multi-organ failure.[7] In a very recent study,[8] despite persistently low MELD-Na scores < 15, patients with cirrhosis still experience high rates of liver related mortality (47.5%) and the most common cause of death was 'infectious'. This is in concordance to our previous studies[9,10] showing a high mortality rate on the Romanian National LT WL and that MELD score at listing in addition to other complications of liver cirrhosis influence survival on the WL. In the present study, our median MELD score at listing was 14 and MELD at inclusion on WL was significantly associated with occurrence of ACLF.

This is the first study applying the new European Association for the Study of the Liver-CLIF consortium criteria to analyze mortality on the WL and early after LT in a group of Romanian cirrhotic patients surviving an episode of ACLF.

ACLF is a complex disease with aggravating liver and kidney function and associated organ failure and elevated short-term mortality (50–90%) in patients with liver cirrhosis even compensated ones and with low MELD scores. Transplantation presents the best outcomes in patients with ACLF that do not recuperate spontaneously or do not ameliorate with supportive measures,[11] representing the only therapeutic option for most of the patients with ACLF.[12] This was proven also in our study, LT being a protective factor for death in ACLF patients. Development of ACLF during waiting on the national WL was associated with significantly lower survival rates, similar to previously reported studies.[2,13] Mortality of patients varies according to ACLF grade in our study similar to those reported in literature. Also improvement is possible after an ACLF episode: 50% from patients with ACLF grade 1 and only 16% of those with grade 3.[5] In our study, ACLF episodes and higher the grade of ACLF were the principle risk factors for death while on the WL. Also kidney and liver failure were among the main reasons of death for patients included on our WL. In a rather recent study, patients with hepatorenal syndrome had a predicted 1-year mortality of 23.5% and overall 1-year mortality of patients on the WL with MELD score <15 was 16% and 23% for MELD > 15.[14] Similarly, in our study, MELD score at inclusion on WL was a predictor of 1-year mortality.

On the other hand, ACLF is associated with a high propensity to infections leading to more complications and poorer prognosis.[15] Bacterial infections carry decisive roles in the development and evolution of ACLF either as a principal precipitating event or a unique complication. In 1 recent study,[16] severe infections (spontaneous bacterial peritonitis, pneumonia, severe sepsis/shock, nosocomial and multiresistant infections) were more common in patients with ACLF. Patients with ACLF and bacterial infections presented higher grade of systemic inflammation at diagnosis, poorer clinical progression and lower 90-day probability of survival (49% vs 72.5%, $P < .001$) than patients with ACLF without infection. In our cohort, development of spontaneous bacterial peritonitis or infections with other localizations was associated with both ACLF occurrence and death on the WL.

Selection of patients with ACLF for LT remains still a controversy and future issues include specific allocation of donor organs to this group of patients that have a comparable risk of mortality to acute liver failure. In the paper of Finkenstedt et al[12] patients who developed infections such as pneumonia and/or sepsis and those who received renal replacement therapy or mechanical ventilation were less likely to undergo LT. That is the reason why, in our LT Program, only patients that improved or recovered after an ACLF episode have been considered for LT. Also the donation rate in Romania is far behind the international rates and discrepancies between need and offer are still important despite the increased donation rate in the years 2015–2017.[17–19] However, in patients surviving an ACLF episode, time to LT was significantly lower compared to patients without ACLF on the WL in relation with the higher MELD scores of these patients compared to non-ACLF patients, concordant with an Austrian study.[12]

This approach, reflecting the policy in the Romanian National LT Program, differs from other previous studies[12,20–22] that analyzed WL mortality and post-LT survival in patients listed and transplanted with ACLF. However, in the above mentioned papers, ACLF is an increasingly significant indication with positive outcome after LT. In the paper of Finkenstedt et al[12] the 1 and 5-year survival rates of 87% and 82% were similar to the rates for non-ACLF patients. However, LT was realizable in less than 1 fourth of the patients with a 5-year survival rate over 80%. In the study by Artru et al[22] even patients with ACLF-3 had a 1-year survival similar to that of patients with a lower grade of ACLF > 80%), although encountered a higher rate of complications and a longer hospital stay. Lower overall 1, 3 and 5 years post-LT graft survival rates were mentioned in studies of living donor liver recipients such as the 1 performed in Korea:[21] in the ACLF group (76.8%, 72.1%, and 70.5%, respectively) compared to the non-ACLF group (89.8%, 82.5%, and 81.0%, respectively) ($P = .035$). However, the patient survival at 1, 3, and 5-years was not statistically different between the ACLF group (79.5%, 73.6%, and 72.1%, respectively) and non-ACLF (90.5%, 83.2%, and 81.8%, respectively) ($P = .063$). Also patients with ACLF-2 and 3, with significantly higher MELD scores tended to demonstrate a worse survival than ACLF-1, but

without reaching a statistical significance. Our results are in agreement with these studies (1-year post-LT patient survival rates ≥80%), although our patients were not transplanted during the ACLF episode and a small proportion of patients were improved from ACLF-3 and transplanted. The low number of patients surviving an ACLF-3 episode is the main limitation of our study.

On the other hand, the study by Levesque et al[23] presented in a subgroup of 30 patients with ACLF grade 3 a 12-month survival rate of 43% after LT. All these studies obviously emphasize that although it is advisable to take into consideration LT in ACLF grade 3, this must be tempered by evaluation of factors that may indicate worse outcome after LT, such as infections, recipient age and presence of hepatocellular carcinoma.[23] Also, in the study of Finkenstedt et al[12] is mentioned that patients who successfully underwent LT had better kidney function, lower MELD scores, lower serum C-reactive protein levels at admission.

In addition, patients with severe weakness due to their advanced liver disease and a persistent inflammatory state, as seen with ACLF, would be expected to be frail and may not be rescued by LT. With this regard, our attitude to transplant patients after amelioration of ACLF has a short and long term good outcome and should be adopted in Transplant Programs with high number of patients on WL and low number of available organs. This concept is proven also by the study of IL-6 that is significantly increased in ACLF patients even in the absence of bacterial infection;[24] also increased IL-6 at reperfusion during LT, serves as valid biomarker of significant early systemic inflammatory response and lower concomitant long term (3 and 5-years) graft and patient survivals.[25]

In conclusion, occurrence of an ACLF episode while on the WL in patients with rather low MELD scores is associated with a significantly higher mortality rate. The number of organ failures (grade of ACLF) influences early mortality. Because LT is the single method that leads to better survival, to improve our capability to detect those patients developing ACLF on the WL who might reverse and then benefit from LT is still a challenge. However, overall survival after LT is comparable to non-ACLF patients in good selected cases.

Author contributions

SI – study design, wrote the paper, clinical results interpretation
MG – completed the data base
IEC – performed statistical analysis, wrote sections of the article
DT, IP, LG – concept of the study, supervised the course of the study, included patients into the study, wrote sections of the article and reviewed the manuscript
GD, DH, VB, CP, RI, CG - included patients into the study, reviewed the manuscript
All authors contributed to manuscript revision, read and approved the submitted version.

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