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***Observational Study***

**Liver transplantation is beneficial regardless of cirrhosis stage or acute-on-chronic liver failure grade: A single-center experience**

Cervantes-Alvarez E *et al*. Liver transplantation benefit in cirrhosis and ACLF

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**ABSTRACT**

***BACKGROUND***

Liver transplantation for the most critically ill remains controversial; however, it is currently the only curative treatment option.

***AIM***

To assess immediate post-transplant outcomes and compare short- and long-term survival among cirrhotic patients stratified by disease severity.

***METHODS***

We included cirrhotic patients undergoing liver transplantation between 2015 and 2019 and categorized them into compensated cirrhosis (CC), decompensated cirrhosis (DC), and acute-on-chronic liver failure (ACLF). ACLF was further divided into severity grades. Our primary outcomes of interest were length of stay in intensive care unit (ICU) and hospital, development of complications, and post-transplant survival at 1 and 6 years.

***RESULTS***

A total of 235 patients underwent liver transplantation (CC = 11, DC = 129 and ACLF = 95). Patients with ACLF had a significantly longer hospital stay [8.0 (6.0–13.0)] d *versus* 6.0 (3.0–7.0) d for CC, and 7.0 (4.5–10.0) d for DC(*P* = 0.01), and developed more infection-related complications (47, 49.5%) *versus* 1 (9.1%) for CC, and 38 (29.5%) for DC (*P* < 0.01). Post-transplant survival at 1 and 6 years was similar among the groups (*P* = 0.60 and *P* = 0.90, respectively). ACLF patients stratified according to ACLF grade [ACLF-1, *n* = 40 (42.1%); ACLF-2, *n* = 33 (34.7%); and ACLF-3, *n* = 22 (23.2%)] had similar length of ICU and hospital stay (*P* = 0.68, *P* = 0.54), as well as comparable frequencies of overall and infectious post-transplant complications (*P* = 0.58, *P* = 0.80). There was no survival difference between ACLF grades at 1 and 6 years (*P* = 0.40 and *P* = 0.15).

***CONCLUSION***

Patients benefit from liver transplantation regardless of cirrhosis stage. ACLF patients have a longer hospital stay and frequency of infectious complications; however, they have excellent, and comparable 1 and 6-year survival rates.

**Key Words:** Liver transplantation; Acute-on-chronic liver failure; Prognosis; Survival analysis; Critical care

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**Core tip:** Patients with cirrhosis classified into compensated or decompensated cirrhosis and acute-on-chronic liver failure (ACLF) underwent liver transplantation. Patients with ACLF had a longer hospital stay and higher frequency of infectious complications, but despite that, they had similar post-transplant survival at 1 and up to 6 years of follow-up.

**INTRODUCTION**

Cirrhosis is the consequence of chronic liver disease caused by a variety of etiological factors, characterized by the disruption of the normal hepatic architecture due to fibrosis with consequent hemodynamic repercussions. Unless the hepatic insult is removed, patients with this condition will suffer progression and transition from a stage of compensated cirrhosis (CC) to a stage of decompensated cirrhosis (DC) with the occurrence of portal-hypertension-related symptoms[[1](#_ENREF_1)]. An entity of recent definition known as acute-on-chronic liver failure (ACLF) is now recognized[[2](#_ENREF_2),[3](#_ENREF_3)], which carries the highest mortality risk given by a state of profound cirrhosis-associated immune dysfunction and the development of organ failure additional to that of the liver[[4](#_ENREF_4),[5](#_ENREF_5)].

Currently, liver transplantation (LT) is the only definitive therapeutic measure for these patients, albeit with the implied risks including post-transplant complications and long-term use of immunosuppressive drugs. However, patients benefit from excellent post-transplant survival.

There is controversial literature, and uncertainty prevails concerning the possible futility of assigning a liver to a patient with advanced cirrhosis and systemic alterations such as in those with ACLF. Some studies have demonstrated the presence of ACLF at the time of LT as a risk factor for mortality and graft loss, and that these patients may have lower short- and long-term survival after LT[[6-8](#_ENREF_6)]. However, others have shown nonsignificant survival differences between ACLF and non-ACLF patients including a marked improvement in the prognosis of those with the highest severity (ACLF-3)[[9-12](#_ENREF_9)]. The development of early allograft dysfunction and renal dysfunction is also comparable between these groups, as well as long-term liver and kidney function[[12](#_ENREF_12),[13](#_ENREF_13)]. However, unfavorable outcomes can be expected and a higher frequency of perioperative and postoperative complications has been reported[[8](#_ENREF_8),[9](#_ENREF_9)]. Differences may be found when ACLF patients are subdivided by ACLF grade; however, survival disparities are still controversial[[7](#_ENREF_7),[9](#_ENREF_9)].

Here, we report the experience of our transplant center in an effort to contribute further to the evidence on the benefit of LT in ACLF. The aim was to assess immediate post-transplant outcomes and to compare the short-term (1 year) and long-term (6 years) post-transplant survival among cirrhotic patients stratified by disease severity. Unlike other studies so far, this study specifically compared survival and outcomes between CC, DC and ACLF, thus distinctly contrasting the extremes of disease severity. Additional analyses were performed to determine possible differences between ACLF grades. These results should encourage further transplantation in those with this severe form of cirrhosis and even in patients with ACLF grade 3.

**MATERIALS AND METHODS**

***Patients and definitions***

This study included all patients undergoing LT between January 1, 2015 and December 31, 2019. Patients with a previous transplant, malignancies other than hepatocellular carcinoma, fulminant hepatic failure, and amyloidosis were excluded. Patients were classified into CC, DC and ACLF, and the latter were further subdivided into ACLF grades 1, 2 and 3 (Figure 1). Diagnosis of CC and DC was based on the absence or presence of symptoms related to portal hypertension, including ascites, encephalopathy, or variceal bleeding, respectively, as previously described[[14](#_ENREF_14)]. All CC patients received LT because of hepatocarcinoma mainly caused by hepatitis C virus (HCV) infection.

ACLF was diagnosed in a patient that fulfilled ACLF criteria any time during their clinical course while waiting to receive an LT according to the EASL-CLIF consortium criteria[[2](#_ENREF_2)], which state the following organ failure (OF) definitions: liver (total bilirubin ≥ 12 mg/dL); kidney (creatinine ≥ 2 mg/dL); brain (encephalopathy grade 3 or 4 according to West–Haven criteria); coagulation (INR ≥ 2.5); circulation (vasopressor use for circulatory failure); and lung (PaO2/FiO2 ≤ 200 or SpO2/FiO2 ≤ 214 or mechanical ventilation caused by lung failure). ACLF grading was performed as follows: ACLF-1, patients with single kidney OF or nonrenal OF plus kidney dysfunction (creatinine 1.5–1.9 mg/dL) and/or brain dysfunction (encephalopathy grade 1 or 2 according to West–Haven criteria); ACLF-2, patients with two OFs; and ACLF-3, patients with three or more OFs.

Patients at our center were considered for LT based on cirrhosis disease severity according to an unrestricted evaluation of the Model for End-Stage Liver Disease (MELD), MELD-Na and CLIF-C scores and were ultimately listed according to an interdisciplinary consensus reached by the gastroenterology, cardiology, pneumology, infectious diseases, otorhinolaryngology, psychiatry, surgery, anesthesiology, and stomatology specialties. LT was mostly carried out with the classic technique. Recipient hepatectomy involved a bilateral subcostal incision with or without midline extension. Then dissection and clamping of the portal vein, hepatic artery, bile duct, and superior and inferior vena cava were performed. Implantation of the donor liver was attained by anastomosing first the superior vena cava from the donor with that of the recipient, followed by the inferior vena cava, and portal vein, after which reperfusion of the donor liver was begun. Total reperfusion was obtained by anastomosing the hepatic artery of the graft with the junction of the gastroduodenal artery and the common hepatic artery of the recipient. The procedure was completed after performing cholecystectomy and duct to-duct anastomosis.

The immunosuppressive regimen in all patients following the procedure consisted of all or a combination of the following drugs: calcineurin inhibitor (tacrolimus or cyclosporine), corticosteroids, mycophenolate mofetil and interleukin-2 receptor antagonist basiliximab. In the event of renal disease in the post-orthotopic liver transplant period, modifications to the immunosuppression regimen including calcineurin inhibitor dose reduction with the addition of mycophenolate mofetil, were performed.

No donor organs were obtained from executed prisoners or other institutionalized people.

This study was approved by the ethics committee of our institution (GAS-2368-17-20) and conformed to the provisions of the Declaration of Helsinki. Requirement for informed consent was waived due to its observational nature.

***Data collection and primary outcomes***

Medical records of all patients were examined to extract the following demographic and clinical variables [gender, age, cirrhosis etiology, presence of ascites and encephalopathy, vasopressor use, PaO2/FiO2 or SpO2/FiO2 relation, requirement of mechanical ventilation and precipitant event (bacterial infection, gastrointestinal hemorrhage, active alcoholism, other or unknown)]. Laboratory data measured at the time of LT necessary to determine disease severity and for the computation of the MELD-Na score were registered: total bilirubin (mg/dL), creatinine (mg/dL), INR, and leukocyte count (× 109/L). Our primary outcomes of interest were: development of immediate post-transplant infectious complications, defined as any type of nosocomial, donor-derived or surgery-related infection during the immediate hospital stay following LT until the patients’ discharge; the development of any type of immediate postoperative complication according to Clavien–Dindo classification[[15](#_ENREF_15)]; and post-LT survival at 1 and 6 years. Similarities in donor liver graft quality were assessed by evaluation of the donor risk index (DRI[[16](#_ENREF_16)]) which considered the donor’s age, height, race and cause of death, donation after cardiac death, split/partial graft, organ allocation and cold ischemia time.

***Statistical analysis***

Results of categorical variables were presented as frequencies and percentages, and as means and standard deviations or medians with interquartile range (IQR) for normally or not normally distributed continuous variables, respectively. Univariate statistical comparisons between categorical variables were performed with Pearson’s χ2 test or Fisher’s exact test, and between continuous variables with the analysis of variance test or the Kruskal–Wallis test according to the normal distribution. Paired *t* tests were carried out between disease severity scores among ACLF groups. Post-transplant survival was analyzed with the Kaplan–Meier method and survival curves were compared with the log-rank test. Statistical analysis was performed with SPSS for Windows version 28.0 (IBM Corp., Armonk, NY, USA) and survival curves were plotted using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org) with the survminer package. Statistical significance was considered at *P* < 0.05.

**RESULTS**

***Non-ACLF and ACLF patient characteristics***

A total of 235 patients that underwent LT from 2015 to 2019 were included in this study, of whom, 95 (38.9%) fulfilled ACLF criteria; 129 (52.9%) were classified as DC, and 11 (4.5%) as CC (Table 1). When compared to the CANONIC study, we identified an overall younger population with ACLF patients being even younger than those with DC and CC [50.0 years [interquartile range (IQR) 37.0–59.0] *vs* 52.0 years (IQR 43.0–61.0) and 57.0 years (IQR 53.0–59.0), respectively; *P* = 0.02]. Autoimmune etiologies (autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis and overlapping syndromes) were the most frequent in ACLF patients (44.2% *vs* 27.9% DC and 9.1% CC; *P* < 0.01), whereas the leading cause in DC and CC patients was HCV infection (72.7% CC, 32.6% DC, and 13.7% ACLF; *P* < 0.0001). With regard to comorbidities, no significant differences were observed between cirrhosis groups for frequencies of either type 2 diabetes mellitus or primary hypertension (*P* = 0.44 and *P* = 0.06, respectively). ACLF patients had the highest MELD-Na score (25 ± 6 *vs* 19 ± 4 and 11 ± 3 for DC and CC, respectively), and accordingly, the highest bilirubin and creatinine values. The presence of clinical ascites and encephalopathy (including West–Haven grade 3/4 encephalopathy) was also significantly higher in ACLF patients (Table 1).

When assessing the last ACLF event of these patients before undergoing LT, the majority were classified as ACLF grade 1 [*n* = 40 (42.1%)] followed by ACLF-2 [*n* = 33 (34.7%)] and ACLF-3 [*n* = 22 (23.2%)] (Table 2). Overall median time to LT since their ACLF event was 31 d (IQR 11.0–88.0). However, those with ACLF-1 had a significantly longer time to LT compared to ACLF-2 and ACLF-3 [54.0 d (IQR 21.3–122.8) *vs* 31.0 d (IQR 7.0–59.5) and 22.0 d (IQR 9.5–46.8), respectively; *P* = 0.03]. Demographic data and etiologies were similar within these three groups, with autoimmune etiologies being the most frequent among all ACLF grades (*P* = 0.30). The most common ACLF precipitants overall were bacterial infections and the absence of an identifiable factor (unknown). Other precipitants including pharmacological and procedure-related complications, were more frequent in ACLF-1 patients (*P* = 0.01). Kidney failure was the only type of OF that did not differ significantly between ACLF groups [18 (45.0%) ACLF-1, 11 (33.3%) ACLF-2, and 14 (63.6%) ACLF-3; *P* = 0.09], whereas liver, brain, coagulation, circulation and lung failure were significantly higher in patients with ACLF-3 (Table 2).

Parameters reflecting disease severity including MELD-Na, CLIF-C OF and CLIF-C ACLF scores, total bilirubin, INR and leukocyte count were higher in ACLF-3 and lower in ACLF-1. We observed a generalized improvement of clinical parameters in ACLF patients at the time of LT, with a concomitant reduction in disease severity scores evaluated. For instance, MELD-Na decreased significantly among all three ACLF grades (*P* < 0.01), and an improvement in the CLIF-C OF score was also observed. CLIF-C ACLF score became similar in ACLF-1, 2 and 3 patients with no significant difference among them (*P* = 0.18), as well as INR and leukocyte count (*P* = 0.05 and *P* = 0.92, respectively) (Table 2).

***ACLF patients have a more complicated post-transplant stay, but comparable short- and long-term survival***

Although severity of cirrhosis clearly differed between CC, DC and ACLF patients, post-transplant outcomes were mostly similar. While total days at the intensive care unit (ICU) were comparable among these groups, patients with ACLF had a significantly longer hospital stay [8.0 d (IQR 6.0–13.0) *vs* 6.0 d (IQR 3.0–7.0) and 7.0 d (IQR 4.5–10.0) in CC and DC, respectively; *P* = 0.01]. The frequency of patients who developed any type of complication (Clavien–Dindo I–V [[15](#_ENREF_15)]) during their immediate hospital stay following LT was also similar; however, those with ACLF more commonly presented with infectious complications (*P* < 0.01) (Table 3). When comparing length of hospital stay and post-transplant outcomes between ACLF grades, no significant differences were observed, thus the clinical course after LT of ACLF-3 patients was similar to that of those with ACLF-1 and 2 (Table 4).

Assessment of post-transplant mortality revealed that ACLF, DC and CC patients have a comparable survival at 1 and 6 years after LT [87 (91.6%), 114 (88.4%), 11 (100%) at 1 year, respectively; *P* = 0.60, and 80 (84.2%), 112 (86.8%), and 10 (90.9%) at 6 years, respectively; *P* = 0.90]. Early transplant mortality at the critical periods of 30 d and 3 mo was also not significant (*P* = 0.38 and *P* = 0.30, respectively).

All groups received the same quality grafts as there were no significant differences between groups in the DRI (*P* = 0.13) (Table 5). Survival as assessed by Kaplan–Meier analysis showed no significant differences among the groups (*P* = 0.79; Figure 2A). These analyses were additionally performed in the ACLF population by subdividing them into their severity grades and there were no significant differences in 30-d and 3-mo mortality (*P* = 0.17 and *P* = 0.65, respectively), and 1-year and overall survival (*P* = 0.40 and *P* = 0.15, respectively). Likewise, no differences were observed in the DRI (*P* = 0.08) (Table 5). This was reflected in a nonsignificant Kaplan–Meier analysis (*P* = 0.17; Figure 2B), which confirmed similar post-transplant outcomes even among ACLF-3 patients.

**DISCUSSION**

Despite controversies, LT has been increasingly encouraged in patients with ACLF, including those with the highest severity grade. Hemodynamic derangements and systemic inflammation may restrain clinicians from considering an ACLF patient as a candidate for this procedure; however, the decision is so urgent that mortality on the waiting list may be even higher than that of status-1a patients[[17](#_ENREF_17)]. In support of LT benefit for critically ill patients, this study demonstrates that according to our single-center experience, post-transplant outcomes in ACLF patients are favorable and in fact comparable with those of CC and DC patients. Even when comparing between ACLF grades, a worse prognosis was not observed in those with ACLF-3.

In contrast to the CANONIC study[[2](#_ENREF_2)], our patient population was younger, and ACLF patients were also the youngest, even though no differences were found according to ACLF grade. However, the main etiology in this group was autoimmune. Although autoimmune diseases in cirrhosis follow a progressive and complicated clinical course, autoimmune ACLF patients in our center showed nonsignificant post-transplant survival differences in comparison with non-ACLF patients, regardless of ACLF grade, which agrees with the excellent survival observed in ACLF patients with autoimmune etiology[[18](#_ENREF_18)]. A clear clinical difference between ACLF, CC and DC patients was evident by a significantly higher MELD-Na score and leukocyte count at the time of the ACLF event. These two parameters, along with the CLIF-C and CLIF C-ACLF, decreased at the time of LT, indicating improvement of the ACLF syndrome and hence a more favorable profile that allowed eventual transplantation. Kim *et al*[[19](#_ENREF_19)] reported that both lower MELD scores and no ACLF progression were independent factors associated with a high survival rate after LT. We also observed that the CLIF-C ACLF score at the time of LT was similar between ACLF grades, which may further explain improvement and thus equally excellent post-transplant outcomes within these subgroups.

Compared to other studies[[9](#_ENREF_9),[20-22](#_ENREF_20)], ACLF-3 patients in our center benefited from an even greater 1-year survival rate (90.9%), which remained higher even after our 6-year follow-up (77.3%). There were several risk factors associated with worse 1-year post-transplant mortality in ACLF-3 patients, such as older age (≥ 53 years), high pretransplant arterial lactate levels, mechanical ventilation, and high leukocyte count (≤ 10 g/L)[[23](#_ENREF_23)]. Contributing to the favorable outcome observed in our ACLF population, including those with ACLF-3, several of the above-mentioned reported risk factors for worse post-transplant mortality were not present in our patients. Our ACLF population was younger and clinical parameters were mostly stable across all severity grades at the time of LT. Leukocyte counts were higher than in DC and CC patients, but generally always lower than 1010/L during the ACLF event or at LT. While bacterial infections were the main ACLF precipitant followed by unknown factors, important differences regarding other cohorts can be found with the frequency of certain OFs. Respiratory failure is a risk factor for lower post-transplant survival[[11](#_ENREF_11),[20](#_ENREF_20),[23](#_ENREF_23)] but was uncommon. Liver failure prevailed in those with severe ACLF, although it was closely followed by extrahepatic OF, including kidney failure, which was the most frequent in those with ACLF-1.

Inevitably, ACLF patients will have a longer and more complicated hospital stay after LT[[9](#_ENREF_9),[22](#_ENREF_22)]. This was true in our center, where the latter required more days in ICU and hospital. Post-transplant complications according to Clavien–Dindo classification[[15](#_ENREF_15)] were no different between ACLF and non-ACLF patients (CC and DC), in accordance with a systematic review[[22](#_ENREF_22)]. Despite this encouraging finding, infectious complications were specifically more common in the former, occurring in over half of them, which is also in agreement with the study of Artru *et al*[[9](#_ENREF_9)]. This may warrant a more directed antibiotic regimen in ACLF patients, and physicians should be aware of this frequent outcome to promote a longer post-transplant survival. Infections were equally prevalent in ACLF-3 patients according to our experience, which may have been because of the similar pretransplant profile identified among severity grades, including nonsignificant CLIF-C ACLF score differences. Good donor liver graft quality, which was comparable among CC, DC and ACLF patients, was another factor that may have contributed to an overall excellent outcome; however, optimal graft quality must not impede the decision for LT, given its lesser impact compared to early transplantation[[24](#_ENREF_24)]. Our results encourage further LT in those with ACLF, considering that this procedure is the only effective treatment option, and that survival was not significantly different in patients with less-advanced cirrhosis, despite a more complicated post-transplant clinical course.

This study was limited by its retrospective nature and its single-center design; hence, findings must be compared with those of other studies. We report here the experience of one of the largest transplant centers in Mexico; however, demographics in this center will vary compared with those in the rest of the country. This may explain the high proportion of autoimmune patients compared with patients with HCV infection or alcoholic hepatitis. Regardless, during the 5-year study period we found a comparable proportion of ACLF patients who underwent LT, whose disease severity was markedly different from that of CC and DC patients. In spite of these differences, we observed a clear LT benefit, as seen in previous studies.

**CONCLUSION**

Out of 235 LT procedures that were carried out between 2015 and 2019 in our center, 38.9% were in ACLF patients. Although important clinical differences were found with non-ACLF patients (CC and DC), and among each other when divided by severity grade, post-transplant survival was uniformly excellent. A longer hospital stay and frequency of infectious complications were to be expected; however, this should not hinder the decision to transplant those with ACLF. Our observations support a benefit even in the most critically ill patients (ACLF-3), given comparable 1- and 6-year survival rates.

**ARTICLE HIGHLIGHTS**

***Research background***

Currently, liver transplantation (LT) is the only definitive therapeutic measure for patients with cirrhosis, albeit with the implied risks including post-transplant complications and long-term use of immunosuppressive drugs. However, these patients benefit from excellent post-transplant survival. The benefit and survival of this procedure for patients with more advanced cirrhosis, such as acute-on-chronic liver failure (ACLF), remain controversial, with some reports showing a clear benefit, while others reporting lower short- and long-term survival after LT.

***Research motivation***

To contribute to the current literature regarding the benefit of LT even in those with more severe diseases, we evaluated the immediate post-transplant outcomes and compared the survival in patients stratified by disease severity.

***Research objectives***

To assess immediate post-transplant outcomes and compare the short-term (1 year) and long-term (6 years) post-transplant survival among cirrhotic patients stratified by disease severity.

***Research methods***

We included cirrhotic patients undergoing LT between 2015 and 2019 and categorized them into compensated cirrhosis (CC), decompensated cirrhosis (DC), and ACLF. ACLF was further divided into severity grades. Medical records of all patients were examined to extract demographic and clinical variables as well as laboratory data measured at the time of LT and in the post-transplant period. Our primary outcomes of interest were: development of immediate post-transplant infectious complications, defined as any type of nosocomial, donor-derived or surgery-related infection during the immediate hospital stay following LT until discharge; the development of any type of immediate postoperative complication according to Clavien–Dindo classification; and post-LT survival at 1 and 6 years. Post-transplant survival was analyzed with the Kaplan–Meier method and survival curves were compared with the log-rank test.

***Research results***

A total of 235 patients underwent liver transplantation (CC = 11, DC = 129 and ACLF = 95). Patients with ACLF had a significantly longer hospital stay and developed more infection-related complications. Post-transplant survival at 1 and 6 years was similar among the groups. When ACLF patients were stratified according to ACLF grade, similar lengths of stay in the intensive care unit and hospital were found, as well as comparable frequencies of overall and infectious post-transplant complications. Despite that, there was no survival difference between ACLF grades at 1 and 6 years.

***Research conclusions***

Patients may benefit from LT regardless of the cirrhosis stage. Despite having a longer hospital stay and a higher frequency of infectious complications, ACLF patients had excellent and comparable 1- and 6-year survival rates.

***Research perspectives***

A multicenter study is required to determine the value of LT in advanced disease patients, such as those with ACLF according to disease etiology.

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**Figure Legends**



**Figure 1 Flowchart of the patients analyzed in this study.** CC: Compensated cirrhosis; DC: Decompensated cirrhosis; ACLF: Acute-on-chronic liver failure.



**Figure 2 Kaplan–Meier analyses for survival after liver transplant between compensated cirrhosis, decompensated cirrhosis, and acute-on-chronic liver failure (A), and between acute-on-chronic liver failure grades (B).** LT: Liver transplant; CC: Compensated cirrhosis; DC: Decompensated cirrhosis; ACLF: Acute-on-chronic liver failure.

**Table 1 Patient characteristics (*n* = 235)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **CC *n* = 11 (4.5%)** | **DC *n*= 129 (52.9%)** | **ACLF *n* = 95 (38.9%)** | ***P* value** |
| Male gender, *n* (%) | 6 (54.5) | 64 (49.6) | 47 (49.5) | 0.95 |
| Age, yr | 57.0 (53.0-59.0)a | 52.0 (43.0-61.0)c | 50.0 (37.0-59.0)a,c | 0.02 |
| Liver cirrhosis etiology, *n* (%) |  |  |  |  |
| Autoimmune | 1 (9.1)a | 36 (27.9)c | 42 (44.2)a,c | < 0.01 |
| HCV | 8 (72.7)a,b | 42 (32.6)b,c | 13 (13.7)a,c | < 0.0001 |
| Alcoholic liver disease |  1 (9.1)  | 11 (8.5) | 9 (9.5) | 0.93 |
| NASH | 0 (0.0) | 7 (5.4) | 6 (6.3) | 0.88 |
| Cryptogenic | 1 (9.1) | 22 (17.1) | 18 (18.9) | 0.76 |
| Other1 | 0 (0.0) | 11 (8.5) | 7 (7.4) | 0.84 |
| Comorbidities, *n* (%) |  |  |  |  |
| Type 2 diabetes mellitus | 3 (27.3) | 22 (17.1) | 13 (13.7) | 0.44 |
| Primary hypertension | 2 (18.2) | 20 (15.5) | 6 (6.3) | 0.06 |
| Pre-transplant clinical data  |  |  |  |  |
| MELD-Na | 11 ± 3a,b | 19 ± 4b,c | 25 ± 6a,c | < 0.0001 |
| Total bilirubin (mg/dL) | 1.18 (1.03-1.45)a,b | 3.39 (2.3-5.46)b,c | 7.70 (4.14-16.63)a,c | < 0.0001 |
| INR | 1.1 (1.1-1.2)a,b | 1.5 (1.3-1.7)b | 1.5 (1.3-2.0)a | < 0.0001 |
| Serum creatinine (mg/dL) | 0.67 (0.57-0.71)a | 0.73 (0.61-0.88)c | 0.97 (0.75-1.35)a,c | < 0.0001 |
| Leukocyte count (× 109/L) | 2.9 (2.4-3)a | 4 (3.1-5)c | 5.4 (3.8-6.8)a,c | < 0.0001 |
| Disease manifestations2, *n* (%) |  |  |  |  |
| Clinical ascites | 0 (0.0)a,b | 88 (68.2)b,c | 88 (92.6)a,c | < 0.0001 |
| Encephalopathy | 0 (0.0)a,b | 69 (53.5)b,c | 80 (84.2)a,c | < 0.0001 |
| Grade 3-4 encephalopathy (West- Haven) | 0 (0.0)a,b | 7 (5.4)b,c | 37 (38.9)a,c | < 0.0001 |

1Includes secondary biliary cirrhosis, drug-induced liver injury, and congenital liver diseases.

2Disease manifestations during the whole clinical course until liver transplantation.

Comparisons between groups are shown with superscript letters.

aSignificant difference between CC and ACLF.

bSignificant difference between CC and DC.

cSignificant difference between DC and ACLF.

ACLF: Acute-on-chronic liver failure; CC: Compensated cirrhosis; DC: Decompensated cirrhosis; HCV: Hepatitis C virus; INR: International normalized ratio; MELD Na: Model for End-Stage Liver Disease-Sodium; NASH: Non-alcoholic steatohepatitis.

**Table 2 Acute-on-chronic liver failure patients characteristics (*n* = 95)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **ACLF-1 *n* = 40 (42.1%)** | **ACLF-2 *n* = 33 (34.7%)** | **ACLF-3 *n* = 22 (23.2%)** | ***P* value** |
| Male gender, *n* (%) | 21 (52.5) | 17 (51.5) | 11 (50.0) | 0.98 |
| Age, yr | 55.0 (39.8-60.0) | 44.0 (36.5-53.0) | 49.0 (37.5-59.3) | 0.14 |
| Time to LT since ACLF event | 54.0 (21.3-122.8)a,b | 31.0 (7.0-59.5)b | 22.0 (9.5-46.8)a | 0.03 |
| Liver cirrhosis etiology, *n* (%) |  |  |  |  |
| Autoimmune | 14 (35.0) | 17 (51.5) | 11 (50.0) | 0.30 |
| HCV | 9 (22.5) | 2 (6.1) | 2 (9.1) | 0.14 |
| Alcoholic liver disease | 2 (5.0) | 4 (12.1) | 3 (13.6) | 0.44 |
| NASH | 3 (7.5) | 2 (6.1) | 1 (4.5) | 0.99 |
| Cryptogenic | 10 (25.0) | 5 (15.2) | 3 (13.6) | 0.50 |
| Other1 | 2 (5.0) | 3 (9.1) | 2 (9.1) | 0.69 |
| ACLF precipitant, *n* (%) |  |  |  |  |
| Bacterial infection | 14 (35.0) | 16 (48.5) | 11 (50.0) | 0.39 |
| Gastrointestinal hemorrhage | 1 (2.5) | 3 (9.1) | 1 (4.5) | 0.44 |
| Active alcoholism | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.99 |
| Other | 10 (25.0)a | 2 (6.1) | 0 (0.0)a | 0.01 |
| Unknown | 15 (37.5) | 12 (36.4) | 10 (45.5) | 0.77 |
| Organ failures, *n* (%) |  |  |  |  |
| Liver | 14 (35.0)a,b | 22 (66.7)b | 16 (72.7)a | < 0.01 |
| Kidney | 18 (45.0) | 11 (33.3) | 14 (63.6) | 0.09 |
| Brain | 5 (12.5)a | 10 (30.3) | 11 (50.0)a | < 0.01 |
| Coagulation | 3 (7.5)a,b | 12 (36.4)b | 11 (50.0)a | < 0.001 |
| Circulation | 0 (0.0)a,b | 8 (24.2)b,c | 14 (63.6)a,c | < 0.0001 |
| Lung | 1 (2.5)a | 3 (9.1) | 7 (31.8)a | < 0.01 |
| ACLF event clinical data |  |  |  |  |
| MELD-Na | 27 ± 4a,b | 29 ± 5b,c | 35 ± 4a,c | < 0.0001 |
| CLIF-C OF | 9 ± 1a,b | 10 ± 1b,c | 12 ± 2a,c | < 0.0001 |
| CLIF-C ACLF | 39 ± 8a | 43 ± 6c | 52 ± 6a,c | < 0.0001 |
| Total bilirubin (mg/dL) | 6.31 (2.99-12.91)a,b | 13.07 (6.39-22.31)b | 23.08 (10.56-27.76)a | < 0.001 |
| INR | 1.5 (1.2-1.9)a,b | 1.9 (1.4-2.5)b | 2.2 (1.7-2.8)a | < 0.001 |
| Serum creatinine (mg/dL) | 1.86 (1.18-2.27)b | 0.93 (0.71-1.99)b,c | 2.25 (1.42-2.87)c | < 0.01 |
| Leukocyte count (× 109/L) | 6.55 (4.73-9.43)a | 6.60 (4.55-8.25)c | 8.75 (6.88-13.05)a,c | < 0.01 |
| Pre-transplant clinical data |  |  |  |  |
| MELD-Na | 23 ± 4a | 25 ± 5c | 29 ± 8a,c | < 0.0001 |
| CLIF-C OF | 8 ± 2a | 9 ± 2 | 10 ± 2a | 0.01 |
| CLIF-C ACLF | 37 ± 9 | 37 ± 8 | 41 ± 12 | 0.18 |
| Total bilirubin (mg/dL) | 4.58 (2.94-8.60)a | 9.75 (5.40-16.62) | 19.59 (5.48-34.11)a | < 0.01 |
| INR | 1.4 (1.3-1.7) | 1.6 (1.3-2.2) | 1.9 (1.4-2.6) | 0.05 |
| Serum creatinine (mg/dL) | 0.96 (0.75-1.29)a | 0.88 (0.72-1.17)c | 1.23 (0.94-1.95)a,c | < 0.01 |
| Leukocyte count (× 109/L) | 4.40 (3.23-6.70) | 4.80 (2.90-6.30) | 4.75 (2.48-10.45) | 0.92 |

1Includes secondary biliary cirrhosis, drug-induced liver injury, and congenital liver diseases.

Comparisons between groups are shown with superscript letters.

aSignificant difference between CC and ACLF.

bSignificant difference between CC and DC.

cSignificant difference between DC and ACLF.

ACLF: Acute-on-chronic liver failure; CLIF-C OF: Chronic Liver Failure Consortium: Organ Failure score; CLIF-C ACLF: Chronic Liver Failure Consortium: acute-on-chronic liver failure score; HCV: Hepatitis C virus; INR: International normalized ratio; MELD Na: Model for End-Stage Liver Disease-Sodium; NASH: Non-alcoholic steatohepatitis.

**Table 3 Post-transplant outcomes (*n* = 235)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **CC, *n* = 11 (4.5%)** | **DC, *n* = 129 (52.9%)** | **ACLF, *n* = 95 (38.9%)** | ***P* value** |
| ICU stay (d)  | 2.0 (1.0-4.0)  | 2.0 (1.5-4.0)  | 3.0 (2.0-5.0)  | 0.05  |
| Hospital stay (d)  | 6.0 (3.0-7.0)a | 7.0 (4.5-10.0)  | 8.0 (6.0-13.0)a | 0.01  |
| Any type of complication, *n* (%) | 7 (63.6) | 105 (81.4) | 85 (89.5) | 0.05 |
| Infectious complications, *n* (%) | 1 (9.1)a | 38 (29.5)b | 47 (49.5)a,b | < 0.01 |
| Complications (Clavien-Dindo), *n* (%) |  |  |  |  |
| I | 4 (36.4)  | 17 (13.2)  | 19 (20.0)  | 0.08 |
| II | 2 (18.2)  | 51 (39.5)  | 32 (33.7)  | 0.31 |
| III | 1 (9.1) | 14 (10.9) | 17 (17.9) | 0.27 |
| IV | 0 (0.0) | 9 (7.0) | 12 (12.6) | 0.23 |
| V | 0 (0.0) | 14 (10.9) | 5 (5.3) | 0.24 |

Comparisons between groups are shown with superscript letters.

aSignificant difference between CC and ACLF.

bSignificant difference between CC and DC.

cSignificant difference between DC and ACLF.

ACLF: Acute-on-chronic liver failure; CC: Compensated cirrhosis; DC: Decompensated cirrhosis; ICU: Intensive care unit.

**Table 4 Acute-on-chronic liver failure post-transplant outcomes (*n* = 95)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **ACLF-1, *n* = 40 (42.1%)** | **ACLF-2, *n* = 33 (34.7%)** | **ACLF-3, *n* = 22 (23.2%)** | ***P* value** |
| ICU stay (d)  | 3.0 (2.0-4.0)  | 3.0 (2.0-6.0)  | 3.0 (2.0-6.0)  | 0.68 |
| Hospital stay (d)  | 8.0 (5.0-11.8) | 8.0 (6.0-15.5)  | 6.0 (5.8-14.3) | 0.54  |
| Any type of complication, *n* (%)  | 35 (87.5) | 31 (93.9) | 19 (86.4) | 0.58 |
| Infectious complications, *n* (%)  | 20 (50.0) | 15 (45.5) | 12 (54.5) | 0.80 |
| Complications (Clavien-Dindo), *n* (%) |  |  |  |  |
| I | 7 (17.5)  | 6 (18.2)  | 6 (27.3)  | 0.62 |
| II | 17 (42.5)  | 11 (33.3)  | 4 (18.2)  | 0.15 |
| III | 5 (12.5) | 7 (21.2) | 5 (22.7) | 0.50 |
| IV | 4 (10.0) | 6 (18.2) | 2 (9.1) | 0.49 |
| V | 2 (5.0) | 1 (3.0) | 2 (9.1) | 0.61 |

ACLF: Acute-on-chronic liver failure; ICU: Intensive care unit.

**Table 5 Post-transplant survival overall and by acute-on-chronic liver failure grade, *n* (%)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **CC *n* = 11 (4.5%)** | **DC *n* = 129 (52.9%)** | **ACLF *n* = 95 (38.9%)** | ***P* value** | **ACLF-1 *n* = 40 (42.1%)** | **ACLF-2 *n* = 33 (34.7%)** | **ACLF-3 *n* = 22 (23.2%)** | ***P* value** |
| DRI  | 1.41 (1.36-2.26)  | 1.38 (1.21-1.53)  | 1.32 (1.19-1.54)  | 0.13  | 1.43 (1.24-1.62)  | 1.27 (1.20-1.43)  | 1.38 (1.20-1.69)  | 0.08 |
| 30-d mortality  | 0 (0.0)  | 10 (7.8)  | 3 (3.2)  | 0.38  | 1 (2.5) | 0 (0.0) | 2 (9.1) | 0.17 |
| 3-mo mortality  | 0 (0.0) | 15 (11.6) | 6 (6.3) | 0.30  | 3 (7.5) | 1 (3.0) | 2 (9.1) | 0.65 |
| 1-yr survival | 11 (100) | 114 (88.4) | 87 (91.6) | 0.60 | 35 (87.5) | 32 (97.0) | 20 (90.9) | 0.40 |
| Overall survival1 | 10 (90.9) | 112 (86.8) | 80 (84.2) | 0.90  | 32 (80.0) | 31 (93.9) | 17 (77.3) | 0.15 |

1Survival was analyzed until 6 years of follow-up, when the study was ended.

ACLF: Acute-on-chronic liver failure; CC: Compensated cirrhosis; DC: Decompensated cirrhosis.



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