ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2022 October 28; 28(40): 5784-5892

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
October 28, 2022

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World J Gastroenterol 2022 October 28; 28(40): 5881-5892

DOI: 10.3748/wjg.v28.i40.5881

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

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

Eduardo Cervantes-Alvarez, Mario Vilatoba, Nathaly Limon-de la Rosa, Osvely Mendez-Guerrero, David Kershenobich, Aldo Torre, Nalu Navarro-Alvarez

Specialty type: Transplantation

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cassese G, Italy; Mogahed EA, Egypt; Sahin TT, Turkey

Received: April 25, 2022
Peer-review started: April 25, 2022
First decision: May 30, 2022
Revised: June 21, 2022
Accepted: September 21, 2022
Article in press: September 21, 2022
Published online: October 28, 2022

Eduardo Cervantes-Alvarez, PECEM, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City 14080, Mexico

Eduardo Cervantes-Alvarez, Nathaly Limon-de la Rosa, Osvely Mendez-Guerrero, David Kershenobich, Aldo Torre, Nalu Navarro-Alvarez, Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City 14080, Mexico

Mario Vilatoba, Department of Trasplant, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City 14080, Mexico

Nalu Navarro-Alvarez, Department of Molecular Biology, Universidad Panamericana School of Medicine, Mexico City 03920, Mexico

Nalu Navarro-Alvarez, Department of Surgery, University of Colorado Anschutz Medical Campus, Denver, CO 80045, United States

Corresponding author: Nalu Navarro-Alvarez, MD, PhD, Assistant Professor, Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga #15, Mexico City 14080, Mexico. nalu.navarroa@incmnsz.mx

Abstract

BACKGROUND

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

AIM

To assess immediate posttransplant outcomes and compare the short (1 year) and long-term (6 years) posttransplant 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 total days of intensive care unit (ICU) and hospital stay, development of complications and posttransplant survival at 1 and 6 years.

RESULTS

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) *vs* CC, 6.0 (3.0-7.0), and DC 7.0 (4.5-10.0); $P = 0.01$] and developed more infection-related complications [47 (49.5%), *vs* CC, 1 (9.1%) and DC, 38 (29.5%); $P < 0.01$]. Posttransplant survival at 1- and 6-years was similar among 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 ICU and hospital stay length ($P = 0.68$, $P = 0.54$), 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 year and 6 years ($P = 0.40$ and $P = 0.15$).

CONCLUSION

Patients may benefit from liver transplantation regardless of the cirrhosis stage. ACLF patients have a longer hospital stay and frequency of infectious complications; however, excellent, and comparable 1 and 6-year survival rates support their enlisting and transplantation including those with ACLF-3.

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

Core Tip: Cirrhotic patients classified into compensated or decompensated cirrhosis and acute-on-chronic liver failure (ACLF) underwent liver transplantation. Patients with ACLF have a longer hospital stay and a higher frequency of infectious complications, but despite that, have similar posttransplant survival at one year and up to 6 years of follow-up.

Citation: Cervantes-Alvarez E, Vilatoba M, Limon-de la Rosa N, Mendez-Guerrero O, Kershenobich D, Torre A, Navarro-Alvarez N. Liver transplantation is beneficial regardless of cirrhosis stage or acute-on-chronic liver failure grade: A single-center experience. *World J Gastroenterol* 2022; 28(40): 5881-5892
URL: https://www.wjgnet.com/1007-9327/full/v28/i40/5881.htm
DOI: https://dx.doi.org/10.3748/wjg.v28.i40.5881

INTRODUCTION

Cirrhosis is the consequence of chronic liver disease originated 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]. An entity of recent definition known as acute-on-chronic liver failure (ACLF) is now recognized[2,3], which imposes the highest mortality risk given by a state of profound cirrhosis-associated immune dysfunction and the development of organ failures additional to that of the liver[4,5].

Currently, liver transplantation (LT) is the only definitive therapeutic measure for any of these patients, albeit with the implied risks including posttransplant complications and the long-term use of immunosuppressive drugs. However, patients benefit in general from excellent posttransplant 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 transplant[6-8]. However, others have shown non-significant 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]. The development of early allograft dysfunction and renal dysfunction is also comparable between these groups, as well as long-term liver and kidney function[12,13]. However, unfavorable outcomes can be expected and a higher frequency of perioperative and postoperative complications has been reported[8,9]. Differences may be found when ACLF patients are subdivided by ACLF grade, however, survival disparities are still controversial[7,9].

We here report our transplant center's experience in an effort to further contribute to the evidence on the benefit of LT in ACLF. The aim was to assess immediate posttransplant outcomes and to compare the short (1 year) and long-term (6 years) posttransplant survival among cirrhotic patients stratified by

disease severity. Unlike other studies so far, this study specifically compares survival and outcomes between compensated, decompensated cirrhosis 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 operational definitions

This study included all patients undergoing LT between January 1st 2015 and December 31st 2019. Patients with a previous transplant, malignancies other than hepatocellular carcinoma, fulminant hepatic failure, and amyloidosis were excluded. Patients were classified into compensated cirrhosis (CC), decompensated cirrhosis (DC), and ACLF, and the latter were further subdivided into ACLF grades 1, 2 and 3 (Figure 1). Diagnoses of CC and DC were based on the absence or presence of symptoms related to portal hypertension, including ascites, encephalopathy, or variceal bleeding, respectively, as previously described[14]. All CC patients received liver transplant because of hepatocarcinoma mainly due to 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 a LT according to the EASL-CLIF consortium criteria[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 due to circulatory failure); and lung ($PaO_2/FiO_2 \leq 200$ or $SpO_2/FiO_2 \leq 214$ or mechanical ventilation due to lung failure). ACLF grading was performed as follows: ACLF-1, patients with single kidney OF or non-renal OF plus kidney dysfunction (creatinine between 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 are 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 are ultimately listed according to an interdisciplinary consensus reached by the gastroenterology, cardiology, pneumology, infectology, otorhinolaryngology, psychiatry, surgery, anesthesiology, and stomatology specialties. Liver transplants were carried out in their majority with classic technique. Briefly, 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 done. Implantation of the donor's 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 then 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.

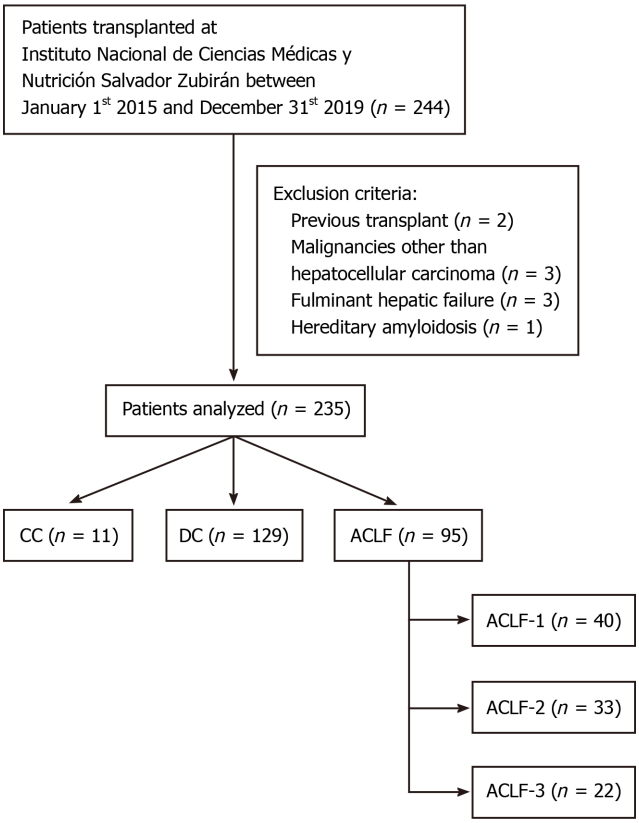
The immunosuppressive regimen in all patients following the procedure consisted of all or a combination of the following drugs: a calcineurin inhibitor (tacrolimus or cyclosporine), corticosteroids, mycophenolate mofetil and the interleukin-2 (IL-2) receptor antagonist basiliximab. In the event of renal disease in the post-orthotopic liver transplant period, modifications to the immunosuppression regimen including CNI dose reduction with the addition of MMF, 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 conforms to the provisions of the Declaration of Helsinki. Requirement of 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, PaO_2/FiO_2 or SpO_2/FiO_2 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 was further registered: total bilirrubin (mg/dL), creatinine (mg/dL), INR, and leukocyte count ($\times 10^9$/L). Our primary outcomes of interest were: the development of immediate posttransplant infectious complications, defined as any type of nosocomial-acquired, donor-derived or surgery-related infection presented 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]; and post-LT survival at 1 year and 6 years. Similarities in donor liver graft quality were assessed by evaluation of the donor risk index (DRI[16]) which considers the donor's age, height, race and cause of death, donation after cardiac death, split/partial graft, organ allocation and cold ischemia time.



DOI: 10.3748/wjg.v28.i40.5881

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

Statistical analyses

Results of categorical variables are 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 Chi-squared 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. Posttransplant survival was analyzed with the Kaplan-Meier method and survival curves were compared with the log-rank test. Statistical analyses were done with SPSS version 28.0 for Windows, IBM Corp., Armonk, NY, United States 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 a P value less than 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 which 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 (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 statistical 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, 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).

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
Other[1]	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 ± 3[a,b]	19 ± 4[b,c]	25 ± 6[a,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 (× 10^9/L)	2.9 (2.4-3)[a]	4 (3.1-5)[c]	5.4 (3.8-6.8)[a,c]	< 0.0001
Disease manifestations[2], *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

[1]Includes secondary biliary cirrhosis, drug-induced liver injury, and congenital liver diseases.
[2]Disease manifestations during the whole clinical course until liver transplantation.
Comparisons between groups are shown with superscript letters.
[a]Significant difference between CC and ACLF.
[b]Significant difference between CC and DC.
[c]Significant 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.

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 (IQR 21.3-122.8) *vs* 31.0 (IQR 7.0-59.5) and 22.0 (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 precipitant 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 OF was the only one 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 of the 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. Interestingly, the CLIF-C ACLF score became similar within 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,

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
Other[1]	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 ± 4[a,b]	29 ± 5[b,c]	35 ± 4[a,c]	< 0.0001
CLIF-C OF	9 ± 1[a,b]	10 ± 1[b,c]	12 ± 2[a,c]	< 0.0001
CLIF-C ACLF	39 ± 8[a]	43 ± 6[c]	52 ± 6[a,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 (× 10^9/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 ± 4[a]	25 ± 5[c]	29 ± 8[a,c]	< 0.0001
CLIF-C OF	8 ± 2[a]	9 ± 2	10 ± 2[a]	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 (× 10^9/L)	4.40 (3.23-6.70)	4.80 (2.90-6.30)	4.75 (2.48-10.45)	0.92

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

Comparisons between groups are shown with superscript letters.
[a]Significant difference between CC and ACLF.
[b]Significant difference between CC and DC.
[c]Significant 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.

respectively) (Table 2).

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

Although severity of cirrhosis clearly differed between CC, DC and ACLF patients, posttransplant outcomes were mostly similar. While total days at the intensive care unit (ICU) were comparable and non-significant 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), CC and DC, respectively; $P = 0.01$]. The frequency of patients who developed any type of complication (Clavien-Dindo I-V complications[15]) during their immediate hospital stay following LT was also similar, however those with ACLF more commonly presented an infectious complication ($P < 0.01$) (Table 3). When comparing days of hospital stay and posttransplant 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 posttransplant 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; $P = 0.60$. 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 non-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 groups ($P = 0.79$; Figure 2A). These analyses were additionally performed in the ACLF population by subdividing them into their severity grades and no significant differences were observed at 30-d and 3-mo mortality ($P = 0.17$ and $P = 0.65$, respectively), 1-year and overall survival ($P = 0.40$ and $P = 0.15$, respectively). Likewise, no differences were observed in the DRI index ($P = 0.08$) (Table 5). This was reflected in a non-significant Kaplan-Meier analysis ($P = 0.17$; Figure 2B), which confirms similar posttransplant 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]. In support of LT benefit for critically ill patients, this study demonstrates that according to our single-center experience, posttransplant outcomes in ACLF are favorable and in fact comparable with those of CC and DC patients. Moreover, even when comparing between ACLF grades a worse prognosis was not observed in those with ACLF-3.

In contrast to the CANONIC study[2], our patient population was in general younger, and interestingly ACLF patients were also the youngest even though no differences were found by ACLF grade. However, the main etiology in this group was of autoimmune nature. Although autoimmune diseases in cirrhosis follow a progressive and complicated clinical course, autoimmune ACLF patients in our center showed non-significant posttransplant survival differences in comparison with non-ACLF patients regardless of ACLF grade, which goes accordingly to the reported excellent survival observed in ACLF patients with autoimmune etiology[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 decrease at the time of LT, indicating improvement of the ACLF syndrome and hence a more favorable profile that allowed eventual transplantation. Indeed, Kim *et al*[19] has previously reported that both lower MELD scores and no ACLF progression are considered independent factors associated with a high survival rate after LT. Moreover, we also observed that the CLIF-C ACLF score at the time of LT was now similar between ACLF grades, which may further explain improvement and thus equally excellent posttransplant outcomes within these subgroups.

Compared to other studies[9,20-22], 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 are several risk factors associated with worse 1-year posttransplant mortality in ACLF-3 patients, such as

Table 3 Posttransplant 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.
[a]Significant difference between CC and ACLF.
[b]Significant difference between CC and DC.
[c]Significant 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 posttransplant 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.

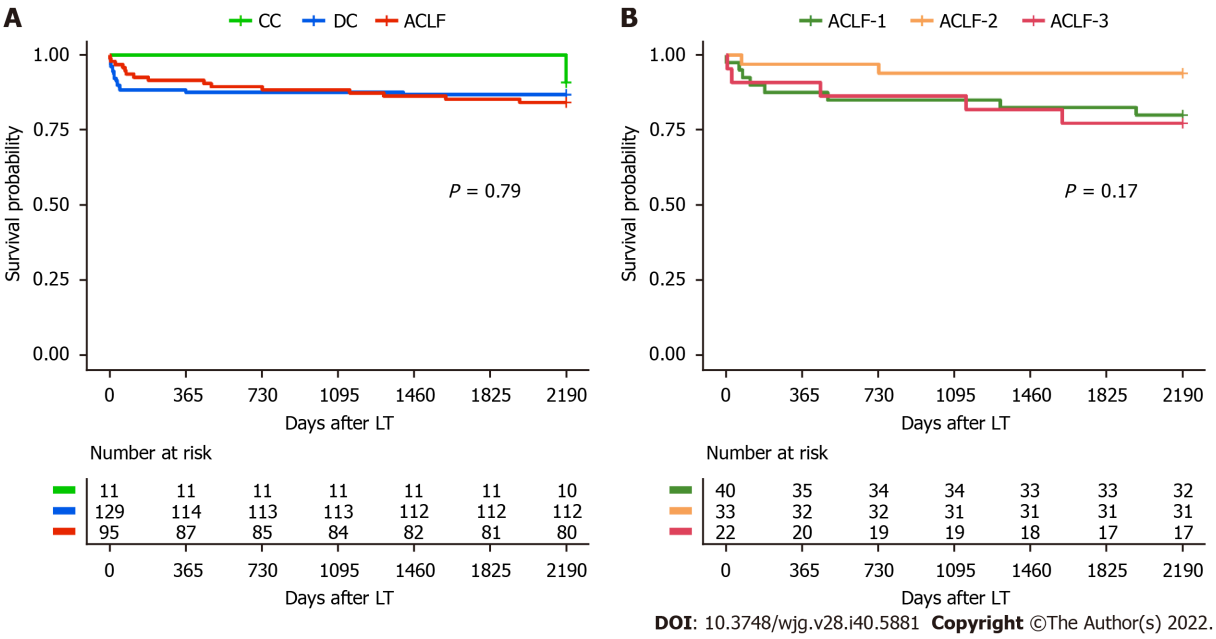
older age (≥ 53 years), high pretransplant arterial lactate levels, mechanical ventilation and high leukocyte count (≤ 10 g/L)[23]. Contributing to the favorable outcome observed in our ACLF population, including those with ACLF-3, several of the above mentioned reported risk factors for worse posttransplant mortality were not present in our patients. First, a younger age characterized our ACLF population 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 10×10^9/L either 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 which is a risk factor for lower posttransplant survival[11,20,23] was uncommon as lung OF seldom occurred. Instead, liver OF prevailed in those with severe ACLF although closely followed by extrahepatic OFs including kidney OF, which was the most frequent in those with ACLF-1.

Inevitably, ACLF patients will have a longer and more complicated hospital stay after LT as has been reported thus far[9,22]. This was true in our center, where the latter required more days of ICU and hospital stay. Posttransplant complications by the Clavien-Dindo classification[15], were not different between ACLF and non-ACLF patients (CC and DC) in accordance with a systematic review[22]. Despite this encouraging finding, infectious complications were specifically more common in the

Table 5 Posttransplant 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 survival[1]	10 (90.9)	112 (86.8)	80 (84.2)	0.90	32 (80.0)	31 (93.9)	17 (77.3)	0.15

[1]Survival 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.



DOI: 10.3748/wjg.v28.i40.5881

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.

former, occurring in over half of them, which is also in agreement with the study of Artru *et al*[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 posttransplant survival. Interestingly, infections were equally prevalent in ACLF-3 patients according to our experience, which may be due to the similar pretransplant profile identified among severity grades including non-significant CLIF-C ACLF score differences. A good donor liver graft quality which was comparable between CC, DC and ACLF patients is 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, as has been recently reported[24]. Overall, our results encourage further transplantation in those with ACLF, considering that this procedure is the only effective treatment option and that survival was not significantly different compared to patients with less advanced cirrhosis, despite a more complicated posttransplant clinical course.

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

previous studies.

CONCLUSION

In conclusion, out of 235 liver transplantation procedures that were carried out between 2015 and 2019 in our center, 38.9% corresponded to ACLF patients. Although important clinical differences were found with non-ACLF patients (CC and DC) and among each other when divided by severity grade, posttransplant survival was uniformly excellent. A longer hospital stay and frequency of infectious complications is to be expected, however, this should not restrain the decision to transplant those with ACLF. Furthermore, our observations support benefit even in the most critically ill patients (ACLF-3), given comparable 1-year 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 posttransplant complications and the long-term use of immunosuppressive drugs. However, these patients benefit in general from excellent posttransplant survival. The benefit and survival of this procedure for patients with more advanced cirrhosis such as those with acute-on-chronic liver failure (ACLF), still remains controversial, with some reports showing a clear benefit, while others reporting lower short and long-term survival after transplant.

Research motivation

In order to contribute to the current literature regarding the benefit of LT even in those with more severe diseases, we evaluate the immediate posttransplant outcomes and compared the posttransplant survival in patients stratified by disease severity.

Research objectives

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

Research methods

We included cirrhotic patients undergoing liver transplantation 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 posttransplant period. Our primary outcomes of interest were: the development of immediate posttransplant infectious complications, defined as any type of nosocomial-acquired, donor-derived or surgery-related infection presented 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; and post-LT survival at 1 year and 6 years. Posttransplant 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. Posttransplant survival at 1- and 6-years was similar among groups. When ACLF patients were stratified according to ACLF grade, similar intensive care unit and hospital stay lengths were found, as well as comparable frequencies of overall and infectious posttransplant complications. Despite that, there was no survival difference between ACLF grades at 1 year and 6 years.

Research conclusions

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

Research perspectives

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

ACKNOWLEDGEMENTS

We would like to thank Elizabeth Costello for her important contribution in editing the English language text of this manuscript.

FOOTNOTES

Author contributions: Cervantes-Alvarez E and Navarro-Alvarez N envisioned the study and wrote the manuscript; Cervantes-Alvarez E, Limon-de la Rosa N and Mendez-Guerrero O supported the data collection and made the formal analysis; Navarro-Alvarez N, Kershenobich D, Vilatoba M, Torre A, Limon-de la Rosa N, Mendez-Guerrero O and Cervantes-Alvarez E reviewed and edited the manuscript; all authors read and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Research Ethics Committee of Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (GAS-2368-17-20).

Informed consent statement: Requirement of informed consent was waived due to the observational nature of this study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Mexico

ORCID number: Eduardo Cervantes-Alvarez 0000-0002-7791-0489; Mario Vilatoba 0000-0002-7141-4337; Nathaly Limon-de la Rosa 0000-0002-1175-3126; Osvely Mendez-Guerrero 0000-0002-9308-9352; David Kershenobich 0000-0001-6178-9170; Aldo Torre 0000-0002-9299-3075; Nalu Navarro-Alvarez 0000-0003-0118-4676.

Corresponding Author's Membership in Professional Societies: American Association for the Study of Liver Diseases, No. 135418.

S-Editor: Gong ZM
L-Editor: A
P-Editor: Gong ZM

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