JGH Open Open Access An open access journal of gastroenterology and hepatology

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.12974

ORIGINAL ARTICLE

Acute on chronic liver failure: A South Australian experience

Shauna Madigan,*,† Yasmina Tashkent,*,† Sharad Trehan,‡ Kate Muller,*,† Alan Wigg,*,† Richard Woodman† and Jeyamani Ramachandran*,†

Departments of *Gastroenterology and Hepatology, ‡General Medicine, Flinders Medical Centre and †College of Medicine and Public Health, Flinders University, Bedford Park, South Australia, Australia

Key words
alcohol use disorder, hepatic encephalopathy, liver failure, organ failure.

Accepted for publication 8 September 2023.

Correspondence
Dr Jeyamani Ramachandran, Department of Gastroenterology and Hepatology, Flinders Medical Centre, and College of Medicine and Public Health, Flinders University, Flinders Drive, Bedford Park, SA 5042, Australia.
Email: jeyamani.ramachandran@sa.gov.au; jeyamani.ramachandran@flinders.edu.au

Declaration of conflict of interest: None.

Abstract

Background and Aim: Acute on chronic liver failure (ACLF) is a clinical syndrome described in patients with acute decompensation (AD) of cirrhosis, characterized by organ failures and high mortality. Intensive management, including liver transplantation (LT), has been shown to improve survival. To address the limited Australian data on ACLF, we describe the prevalence, clinical profile, and outcome of ACLF in an Australian cohort of hospitalized patients.

Methods: A retrospective review of hepatology admissions in a tertiary hospital from 1 January 2017 to 31 December 2019 identified AD and ACLF cohorts, as defined by the European Association for Study of the Liver definition. Patient characteristics, clinical course, survival at 28- and 90-day survival, and feasibility of LT were analyzed.

Results: Among the 192 admissions with AD, 74 admissions (39%) met ACLF criteria. A prior diagnosis of alcohol-related cirrhosis was highly prevalent in both cohorts. Grade-1 ACLF was the most frequent (60%), with renal failure being the commonest organ failure; 28-day (23% *vs* 2%, $P = <0.001$) and 90-day mortality (36% *vs* 16%, $P = 0.002$) were higher in ACLF than AD. Due to ongoing alcohol use disorder (AUD), only six patients underwent LT assessment during ACLF admission.

Conclusion: ACLF was common in our cohort of cirrhosis with AD and was associated with high mortality. AUD despite prior cirrhosis diagnosis was a barrier to LT. Prioritization of ACLF patients for LT after addressing AUD and relaxation of the 6-month abstinence rule may improve ACLF survival and should be addressed in prospective studies.

Introduction

Cirrhosis of the liver is an advanced chronic liver disease (CLD) caused commonly by alcohol, obesity, and hepatitis viruses.[1] The health and economic burden attributable to CLD has been steadily increasing over the past decade worldwide. In Australia, the number of affected people is estimated to exceed 8 million by 2030.[2] In its decompensated stage, liver cirrhosis is characterized by multiple and recurrent complications such as refractory ascites, hepatorenal syndrome (HRS), and hepatic encephalopathy (HE), resulting in frequent hospital admissions that contribute to significant morbidity and mortality.[1,3] Acute on chronic liver failure (ACLF) is a distinct clinical syndrome that is encountered in patients with acute decompensation (AD) of cirrhosis and is associated with a high short-term mortality.[4] It is characterized by intense systemic inflammation that occurs in association with a precipitating event. Pro-inflammatory events that have been identified to precipitate ACLF include alcoholic hepatitis, infections like spontaneous bacterial peritonitis (SBP), and gastrointestinal (GI) bleeding.[5,6] The ensuing inflammation results in single or multiple organ failures. Commonly encountered organ failures affect liver, kidney, brain, and lung, as well as coagulation and circulation.[4,5] ACLF is defined by various international definitions and diagnostic criteria. The European Association for the Study of the Liver—Chronic Liver Failure (EASL-CLIF) defines ACLF based on organ failures and stratifies ACLF into three grades depending on the number of organ failures.[7] North American Consortium for the Study of End-Stage Liver Disease (NACSELD) defines ACLF with two or more extra hepatic organ failures.[8] However, extrahepatic organ failures are not included in The Asian Pacific Association for the Study of the Liver–ACLF Research Consortium (AARC) definition.[9]

Defining ACLF as a separate entity from AD, risk stratifies a subgroup of patients who will benefit from aggressive supportive management and early identification for liver transplantation (LT). This has been addressed by multiple researchers worldwide in various settings ranging from

hepatitis-B-specific causes of ACLF in Asian populations to large hospital-based cohorts from the United States.[4,7,10,11] While the utility and futility of LT in ACLF need to be carefully considered, many studies have reported excellent (>80%) 1-year survival rates in carefully selected patients with advanced ACLF grade 3.[12–14]

Thus, with the improvement in the understanding of the pathogenesis, natural history, and management of ACLF, transplant centers worldwide are increasingly aware of the need to prioritize ACLF for LT after careful evaluation. This study was undertaken to address the limited Australia data on ACLF. The aims of this study were to investigate the prevalence, precipitants for organ failures, grades of ACLF, outcomes including 28- and 90-day survival, and feasibility of LT in an Australian cohort of hospitalized patients with ACLF.

Methods

In this retrospective study, cirrhotic patients admitted to the Hepatology Unit at Flinders Medical Centre were studied. Flinders Medical Centre is a publicly funded tertiary liver transplant center in Adelaide, South Australia. The study cohort was identified using ICD-10 coding terms and applying to hepatology admissions from 1 January 2017 to 31 December 2019. ICD-10 codes used were as follows: alcoholic liver disease (K70), alcoholic hepatitis (K701), alcoholic cirrhosis of the liver (K703), alcoholic hepatic failure (K704), alcoholic liver disease unspecified (K709), hepatic failure (K72), acute and subacute hepatic failure (K720), hepatic failure unspecified (K729), HRS (K767), ascites (R18), SBP (K65.2), esophageal variceal bleeding (I85.01), HE (K72.90), and acute kidney failure unspecified (N17.9). This process generated a list of 859 admissions.

Figure 1 shows the study flow and criteria for inclusion and exclusion. Admissions that were excluded were short-term elective admissions, those unrelated to complications of cirrhosis, admissions outside the hepatology unit, and those with no evidence of CLD (imaging or biochemical). Remaining admissions were then assessed to see whether patients fulfilled criteria for ACLF as defined by the EASL-CLIF Consortium and CLIF-C-ACLF score calculator.[15] This score was calculated for each patient at the time of admission (day 0) and then at day 3. Patient admissions were then divided into two cohorts: those who fit criteria for ACLF (labeled ACLF) and those who did not (labeled AD).

For both cohorts, information was collected from patient medical records including age, sex, etiology of CLD, and comorbidities. Hematology and biochemical tests were recorded

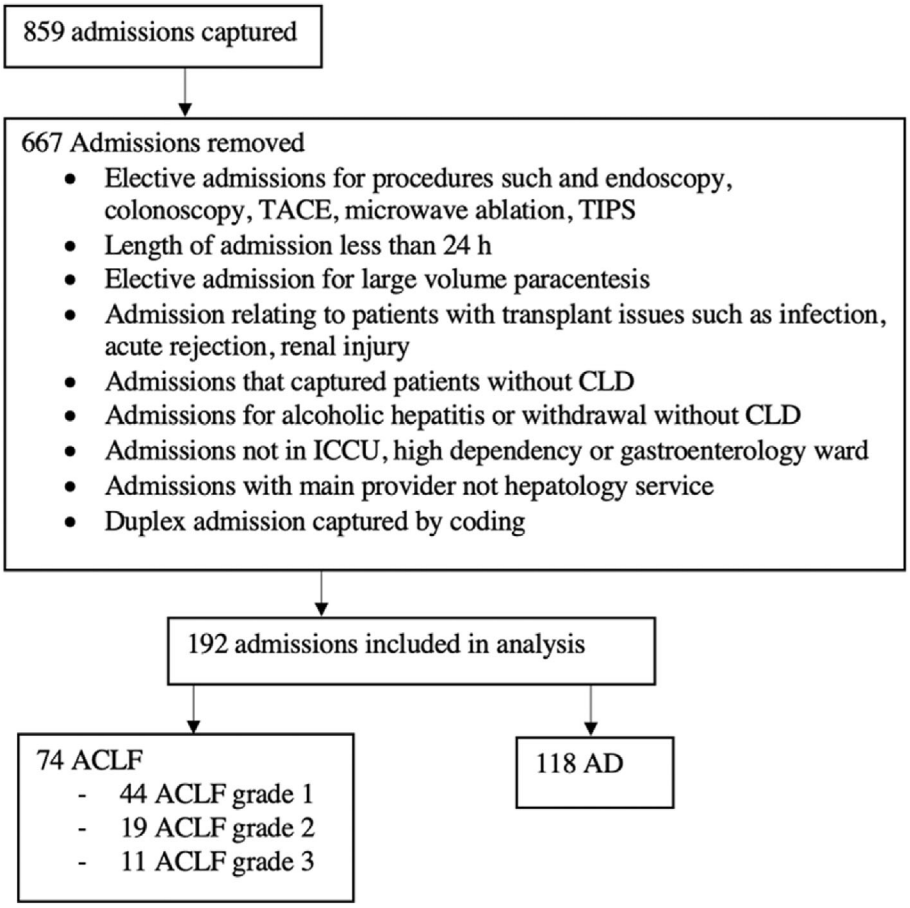

Figure 1 Study flowchart showing inclusion and exclusion criteria. ACLF, acute on chronic liver failure; AD, acute decompensation; CLD, chronic liver disease, ICCU, intensive and critical care unit, TACE, transarterial chemo embolization,TIPS, transjugular intrahepatic porto systemic shunt

including serum sodium, bilirubin level, creatinine, coagulation studies, platelet count, white cell count (WCC), and C-reactive protein (CRP). Mayo Clinic Model for End-stage Liver Disease (MELD) score was calculated for each patient, and mortality at 28 and 90 days was analyzed. Data on the presence of HE, ascites, bleeding events, and infection, as well as requirements for intensive care support, such as mechanical ventilation, renal replacement therapy, and vasopressors, were obtained from medical records. For the ACLF cohort, additional data including precipitant for ACLF, organ failures, referral for LT, and LT outcomes were recorded.

Statistical analysis. Continuous data were described using mean and SD for normally distributed data, and median and interquartile range for non-normally distributed data. Categorical data were reported using frequencies and percentage. Independent *t*-tests, chi-squared tests, or Fisher's exact test were used to compare patient characteristics as appropriate using a two-sided Type 1 error rate of alpha = 0.05. Differences in the cumulative incidence of mortality at 28 and 90 days from the initial hospital admission were assessed using Fisher's exact test. Differences in the transplantation-free survival rate at 28 and 90 days from the initial admission between ACLF and AD were described using the Kaplan–Meier method and compared for statistical significance using a log-rank test. IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA) and Stata (StataCorp, version 17.0) were used for the statistical analysis and graphs.

The study was approved by the Southern Adelaide Human Research Ethics Committee reference number: LNR/56/SAC/21.

Table 1 Comparison of demographic and clinical characteristics between acute on chronic liver failure (ACLF) and acute decompensation of chronic liver disease (AD)

	ACLF ($n = 74$)	AD ($n = 118$)	*P*-value
Age, years, mean ± SD	54 ± 11	59 ± 13	0.013
Male sex, *n* (%)	58 (78)	91 (71)	0.86
Etiology of cirrhosis, *n* (%)			0.34
Alcohol	51 (69)	72 (61)	
NASH	5 (7)	12 (10)	
HCV	5 (7)	4 (3)	
Multiple etiology[†]	11 (15)	19 (6)	
Miscellaneous[‡]	2 (3)	11 (9)	
Known cirrhosis prior to admission, *n* (%)	67 (91)	99 (84)	0.27
Serum CRP, mg/L, mean ± SD	23 ± 23	25 ± 28	0.512
White cell count, $\times 10^9$/L, mean ± SD	9.56 ± 6	8.00 ± 4	0.055
Bilirubin, μmol, mean ± SD	103 ± 110	62 ± 57	0.001
INR, mean ± SD	2.1 ± 0.7	1.6 ± 0.3	< 0.001
CLIF-C AD score, mean ± SD		54 ± 8.4	
MELD, mean ± SD	27 ± 7	19 ± 6	< 0.001
Charlson comorbidity index, mean ± SD	5 ± 2	5 ± 2	0.406
Length of stay, median days (IQR)	11 (11)	5 (7)	0.01

[†]Various combinations of non-alcoholic fatty liver disease, alcohol, hepatocellular carcinoma.
[‡]Cryptogenic, alpha antitrypsin, biliary atresia, primary biliary cholangitis, biliary strictures, and autoimmune hepatitis.
CLIF-C AD score, Chronic Liver Failure Consortium Acute Decompensation score; CRP, C-reactive protein; HCV, hepatitis C virus; INR, international normalized ratio; IQR, interquartile range; NASH, non-alcoholic steatohepatitis; MELD, Model for End-stage Liver Disease.

Table 2 Comparison of demographic and clinical characteristics between acute decompensation of chronic liver disease (AD) that progressed to acute on chronic liver failure (ACLF) and AD

	Pre-ACLF (8)	AD (118)	*P*-value
Age, years, mean ± SD	51 ± 9	59 ± 13	0.14
Male sex, *n* (%)	7 (87)	91 (71)	0.49
Known cirrhosis, *n* (%)	7 (87)	99 (84)	0.78
Alcohol related cirrhosis, *n* (%)	5 (62.5)	72 (61)	0.9
Bilirubin, μmol, mean ± SD	104 ± 72.2	62 ± 84.6	0.054
INR, mean ± SD	2.4 ± 0.08	1.6 ± 0.3	<0.001
MELD, mean ± SD	25.3 ± 6.8	18.9 ± 5.7	<0.001
CRP, CRP mg/L, mean ± SD	9.6 ± 8.6	25.4 ± 28.3	0.15
CLIF-C AD score, mean ± SD	59.5 ± 8.9	54.0 ± 8.4	0.08

CLIF-C AD score, Chronic Liver Failure Consortium Acute Decompensation score; CRP, C-reactive protein; INR, international normalized ratio; MELD, Model for End-stage Liver Disease.

Results

During the study period, 112 patients experienced a total of 192 admissions with an AD of cirrhosis; 667 admissions were excluded (Fig. 1). Based on the EASL-CLIF criteria, 74 admissions (39%) were identified to represent ACLF, and the remaining 118 admissions without ACLF were classified as AD (61%).

Patient characteristics of both study groups are given in Table 1. ACLF patients were younger, had higher MELD scores and longer hospital stay compared with AD patients. Of the 74 ACLF admissions identified, the majority (89%) had ACLF on admission and the remaining 11% developed ACLF on day 3. Demographic characteristics and liver disease severity were compared between those admissions that progressed to ACLF within 3 days of hospital admission and those who stayed as AD, as shown in Table 2. MELD and INR were significantly higher in pre-ACLF patients. CLIF-AD score was higher although not statistically significant.

Alcohol-related liver disease (ARLD) was the most common cause of underlying cirrhosis. The majority of patients (91% and 84%) had known cirrhosis prior to admission with ACLF and AD, respectively. At this center, patients with cirrhosis are managed within a chronic disease management program known as the Chronic Liver Failure Program (CLFP) coordinated by specialist liver nurses. In the ACLF cohort, 86% patients were already enrolled in the CLFP and so were 55% of the AD cohort.

Of the ACLF cohort, 31 admissions (42%) required transfer to the critical care unit compared with 7 admissions (6%) in the AD cohort. In the ACLF cohort, 15 (20%) admissions required intubation, 16 (22%) patients required inotropic support, and 6 (8%) required renal replacement therapy. This contrasted with the AD cohort, where only one patient required mechanical intubation, one patient required inotropic support, and none required renal replacement therapy.

Precipitants for ACLF were as follows: infection (30%), unknown precipitant (26%), upper GI bleed (18%), active alcohol use (16%), multiple precipitants (8%) and post-paracentesis circulatory dysfunction (3%). Grade 1 ACLF was the most frequent (60%), with renal failure being the most common organ failure (46%) (Table 3).

Of the 112 patients, 78 patients had a single admission during the study period (28 with ACLF and 50 with AD), 3 patients had recurrent admissions with ACLF, 12 had recurrent admissions with AD, and 4 had a combination of AD and ACLF. Interestingly, 14 patients who were admitted with AD later developed ACLF within a mean duration of 72 days. Four of these 14 patients died within 90 days of hospital admission.

Mortality at 28 and 90 days of admission was higher in ACLF patients. At 28 days of admission, the difference in mortality rate between ACLF (17/74, 23%) and AD (2/118, 2%) was significant, $P < 0.001$. A similar trend was seen at 90 days as well, with mortality rate for ACLF (27/74, 37%) significantly higher than AD (19/118, 16%), $P = 0.020$. Survival functions using Kaplan–Meier curves and differences in survival rates in ACLF and AD compared using log-rank test are shown in Figure 2.

Referral for liver transplantation. From the ACLF cohort, 15 patients were referred for LT. Of these, only four referrals were made during the ACLF admission, nine were already referred prior to ACLF admission, and two were referred in a subsequent clinic review or admission. Of these 15 patients, 8 had LT: 7 had grade-1 ACLF and 1 had grade-2 ACLF. One-year survival after LT was 88%. Of the 59 patients not referred for LT assessment, 51 patients (86%) had ARLD and 31 of these patients (60%) were documented to have active alcohol consumption.

Table 3 Characteristics of acute on chronic liver failure (ACLF)

ACLF grade 1	
Organ failure, total	44 (60%)
Single kidney failure	25 (45.5%)
Single liver, coagulation, circulatory or respiratory failure + creatinine 1.5–1.9 mg/dL and/or HE I–II	15 (33.3%)
Single cerebral failure (HE III–IV) + creatinine 1.5–1.9 mg/dL	4 (9.1%)
MELD, mean ± SD	25.5 ± 6.1
CLIF-C score, mean ± SD	43.3 ± 7.5
28-Day mortality, *n* (%)	11/44 (25%)
90-Day mortality, *n* (%)	18/44 (40%)
ACLF grade 2	
Organ failure, total	19 (25%)
Brain and kidney	7 (36.8%)
Coagulation and liver	5 (26.3%)
Renal and circulation	2 (10.5%)
Renal and coagulation	2 (10.5%)
Other combinations	3 (15.8%)
MELD, mean ± SD	28 ± 6.0
CLIF-C score, mean ± SD	48.2 ± 7.4
28-Day mortality, *n* (%)	3/19 (16%)
90-Day mortality, *n* (%)	4/19 (21%)
ACLF grade 3	
Organ failure, total	11 (15%)
Lung, brain, circulation	3 (27.3%)
Brain, coagulation, liver	2 (18.2%)
Coagulation, liver circulation	2 (18.2%)
Other combinations	4 (36.4%)
MELD, mean ± SD	30.8 ± 11.4
CLIF-C score, mean ± SD	59.9 ± 7.4
28-Day mortality, *n* (%)	3/11 (27%)
90-Day mortality, *n* (%)	5/11 (45%)

CLIF-C AD score, Chronic Liver Failure Consortium Acute Decompensation score; HE, hepatic encephalopathy; MELD, Model for End-stage Liver Disease.

Discussion

The aim of this study was to describe the clinical profile of ACLF in an Australian cohort in the current milieu of improving LT outcomes and supportive treatments for ACLF. Region-specific data on ACLF are essential for early identification and

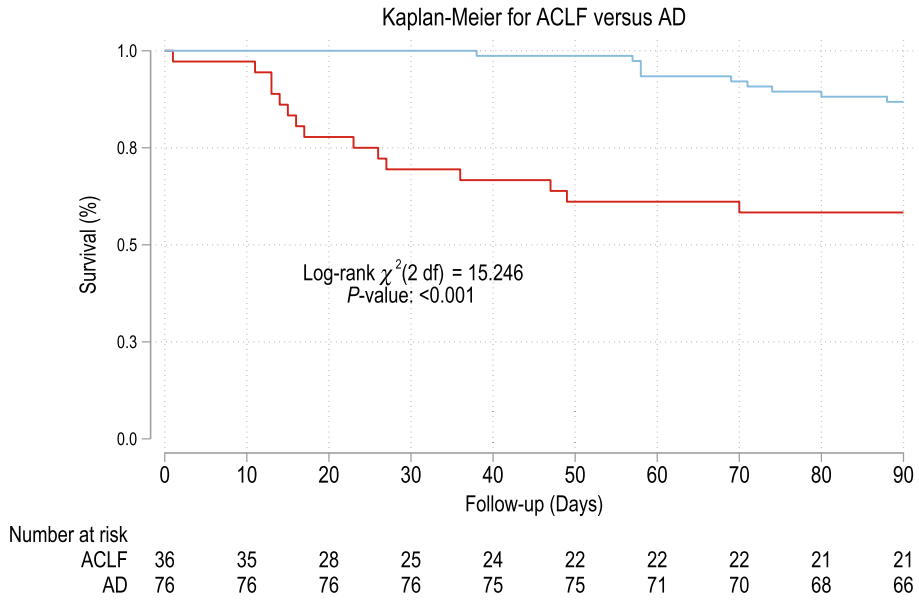

Figure 2 Kaplan–Meier curves and differences in survival rates in acute on chronic liver failure (ACLF) and acute decompensation (AD) of cirrhosis compared using log-rank test. (——), ACLF; (——), AD

intensification of management protocols based on the prevailing causes and precipitants.[16]

ACLF accounted for 39% of admissions in patients with acutely decompensated cirrhosis, a figure much higher than the reported European data of 22%.[4] This could have been due to the referral bias of our center being a specialized liver unit as shown by a similar Australian study (published in abstract form) showing a 34% prevalence of ACLF among patients admitted with AD.[17] Consistent with the available literature, our ACLF patients were younger, had higher MELD scores, were more likely to require admission to the intensive care unit (ICU) for inotropic support/mechanical ventilation/renal replacement therapy, and experienced longer lengths of stay.

The demographic characteristics of our cohort were similar to North American and European cohorts.[4,18,19] Similar to the CANONIC study cohort, the majority of patients were known to have cirrhosis prior to the episode of hospital admission with ACLF. In our population, the leading cause of cirrhosis was ARLD (69%) similar to that reported from the European, Asia-Pacific, and American populations at 60.3%, 56%, and 42%, respectively.[20] In our population, the most common precipitant for ACLF was infection (30%), and the cause was unknown in 25%. In the CANONIC study cohort, the precipitant for ACLF was unknown in 40% of cases,[4] whereas a Chinese cohort study had relapse of hepatitis B as the leading cause.[21]

The most frequently encountered grade of ACLF in our population was of grade 1 (60%), with kidney failure being the commonest organ failure (46%) mirroring the CANONIC study. This was followed by ACLF grade 2 (26%) with combined brain and kidney failure. In patients with ACLF, the 28- and 90-day transplant-free mortality was 23% and 36%, respectively. Compared with the reported mortality of 32% at 1 month and 56% at 3 months in the CANONIC study, the mortality rates observed in our study were lower.[4] Gustot *et al*. reported increasing mortality rates with an increase in grade of ACLF with grade 3 experiencing a short-term mortality between 68% and 89%.[22] In contrast, the mortality rates in our patients with ACLF grades 2 and 3 were not higher than that of grade 1. It is possible that the lower mortality rates observed could be attributed to the intensive outpatient monitoring of patients within the CLFP associated with our hospital, which may have captured early presentations leading to intervention before marked deterioration. However, due to the smaller numbers of patients with advanced ACLF and single-center retrospective study design, these findings should be interpreted with caution. Nevertheless, the high overall short- and intermediate-term mortality in ACLF demonstrated by this study underpins the importance of early identification of the condition and escalation of management.

The current treatment goals for ACLF are early recognition, treatment of precipitating events, supportive therapy, and early LT referral. Recent data have shown that emergent transplant in ACLF provided significantly better overall survival benefit compared with no LT (80% *vs* 16%).[23] Similarly, a recent large collaborative study from Europe has also confirmed the benefit of LT in ACLF with a 1-year post-LT survival of 80%, even for advanced ACLF, compared with much lower 1-year survival on the waiting list of 50%.[24] Several prognostic factors such as pre-LT arterial lactate level ≥ 4 mmol/L, mechanical ventilation with $PaO_2/FiO_2 \leq 200$ mmHg, pre-LT leucocyte count ≤ 10×10^9/L, and drug-resistant infections were associated with poor survival after LT and liver transplant futility.[12,24] However, ACLF grade-3 patients, with the worst survival without LT, are not reliably identified by high MELD, as shown in a UNOS registry study,[25] although LT within 30 days of listing improved their survival. Further demonstration of a higher wait list mortality of ACLF grade 3 than that of status-1a patients supports the

cause for prioritization of ACLF patients for LT.[26] Nevertheless, reports of high-resource utilization with prolonged ICU stay and compromised graft and patient survival after LT in ACLF cannot be ignored.[27] Before adopting early LT in ACLF, a number of outstanding concerns will need to be addressed, including long-term survival and quality of life after LT, ideal LT timing, details of waiting list survival, and ideal organ allocation systems. These questions may be answered by the ongoing prospective international multicenter CHANCE study comparing survival of patients with ACLF grades 2 and 3 undergoing LT with that of patients with decompensated cirrhosis without ACLF.[28]

In addition, our observation of a high proportion of patients with ACLF on a background of ARLD and active alcohol consumption raises the importance of addressing management of alcohol use disorder (AUD) before LT referral. Transplantation Society of Australia & New Zealand (TSANZ) guidelines for LT require a 6-month period of abstinence from alcohol before LT referral.[29] AUD posed a barrier to transplant referrals and, thus, fewer LT for ACLF in our study cohort. Without improvement in resources and management strategies for AUD, ACLF patients will continue to have poor outcomes. Suggestions to improve the current situation include increased resourcing for integrated addiction services associated with liver transplantation units to allow the provision of on-site addiction specialists and alcohol relapse prevention therapies, such as cognitive behavioral therapy and pharmacotherapy, to manage AUD before and after liver transplant.[30,31] It is also desirable that AUD management is planned at the time of diagnosis of ARLD and not at the time of listing for LT or ACLF. The responsibility for addressing AUD should be shared by primary care practitioners and hepatologists.

A further suggestion is the removal of the 6-month alcohol abstinence rule for alcohol-related cirrhosis before LT in the context of improved and integrated addiction services. This arbitrary threshold of abstinence is controversial and is not a strong predicator of relapse reduction.[32,33] Early LT performed for carefully selected severe alcoholic hepatitis (SAH) patients with favorable psychosocial and clinical profile without 6 months of abstinence was shown to have lower rates of harmful alcohol relapse post LT without any reduction in post-LT survival.[34–37] In fact, a recent meta-analysis of patients who underwent LT for SAH has revealed an alcohol relapse rate of 14%, similar to those undergoing elective LT for alcohol-related cirrhosis.[38] Accordingly, the updated TSANZ guidelines approve early LT for SAH in patients with a favorable psychosocial profile with a strong recommendation for management of AUD with a multidisciplinary approach.[29] Similarly, in patients with alcohol-related cirrhosis, evidence is accumulating in support of early LT without the mandatory 6-month abstinence. A cohort study that compared early LT (less than 6-month abstinence) and standard LT (with 6-month abstinence) in patients with alcohol-related cirrhosis highlighted similar outcomes in relapse-free survival and overall graft function in both the groups.[39] Correspondingly, positive outcomes for LT in alcohol-related cirrhosis, without the 6-month rule, has been reported with the use of a pilot program that incorporated social support in addition to pre- and post-addiction treatment.[40] Hence, the condition of 6-month mandatory alcohol abstinence before LT needs to be re-evaluated in Australia for patients with alcohol-related cirrhosis with a structured plan for management of AUD in place.

This study is the first detailed report of ACLF in an Australian cohort. The frequent occurrence of ACLF on a prior diagnosis of ARLD is topical given the recent recognition of noninferior outcomes for early LT for the same. However, the limitation of retrospective design of the study with reliance on patient records is acknowledged. Finally, the CLFP associated with our unit, which has been shown to reduced emergency admissions,[3] may have reduced the incidence of ACLF in our patients, and our study outcomes may not be representative of the actual burden of the problem in other Australian units.

These limitations can be addressed by a prospective multicenter study to define the burden of ACLF among patients presenting with AD. Given the improved long-term survival after LT in patients with ACLF,[13] it is essential to expedite evaluation of these patients for LT and identify barriers to successful LT. Implementation of a multidisciplinary approach with an addiction specialist and counselors operating within the liver unit is highly recommended to address AUD before and after LT to decrease relapse and improve outcomes.

In conclusion, ACLF was common in our cohort of cirrhosis with AD and was associated with high short- and intermediate-term mortality without LT. Ongoing alcohol use despite prior cirrhosis diagnosis was a major barrier that limited transplant referrals. Our study identifies an urgent need to integrate the management of AUD in cirrhosis care to improve the feasibility of LT in patients with ARLD and ACLF. Multicenter prospective studies that evaluate patient selection and organ allocation in ACLF patients for LT without the prevailing 6-month abstinence rule for ARLD are essential to improve patient outcomes in ACLF.

References

1 Ge PS, Runyon BA. Treatment of patients with cirrhosis. *N. Engl. J. Med.* 2016; **375**: 2104–5.
2 Deloitte Access Economics. *The Economic Cost and Health Burden of Liver Diseases in Australia*, Gastroenterological society of Australia and Australian Liver Association, Australia; 2013.
3 Ramachandran J, Hossain M, Hrycek C *et al*. Coordinated care for patients with cirrhosis: fewer liver-related emergency admissions and improved survival. *Med. J. Aust.* 2018; **209**: 301–5.
4 Moreau R, Jalan R, Gines P *et al*. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013; **144**: 1426–1437.e1–9.
5 Arroyo V, Moreau R, Jalan R. Acute-on-chronic liver failure. *N. Engl. J. Med.* 2020; **382**: 2137–45.
6 Zaccherini G, Weiss E, Moreau R. Acute-on-chronic liver failure: definitions, pathophysiology and principles of treatment. *JHEP Rep.* 2021; **3**: 100176.
7 Jalan R, Saliba F, Pavesi M *et al*. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J. Hepatol.* 2014; **61**: 1038–47.
8 O'Leary JG, Reddy KR, Garcia-Tsao G *et al*. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. *Hepatology*. 2018; **67**: 2367–74.
9 Sarin SK, Choudhury A, Sharma MK *et al*. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. *Hepatol. Int.* 2019; **13**: 353–90.

10 Li H, Chen LY, Zhang NN *et al*. Characteristics, diagnosis and prognosis of acute-on-chronic liver failure in cirrhosis associated to hepatitis B. *Sci. Rep.* 2016; **6**: 25487.
11 Hernaez R, Kramer JR, Liu Y *et al*. Prevalence and short-term mortality of acute-on-chronic liver failure: a national cohort study from the USA. *J. Hepatol.* 2019; **70**: 639–47.
12 Artzner T, Michard B, Weiss E *et al*. Liver transplantation for critically ill cirrhotic patients: stratifying utility based on pretransplant factors. *Am. J. Transplant.* 2020; **20**: 2437–48.
13 Trebicka J, Sundaram V, Moreau R, Jalan R, Arroyo V. Liver transplantation for acute-on-chronic liver failure: science or fiction? *Liver Transpl.* 2020; **26**: 906–15.
14 Artru F, Louvet A, Ruiz I *et al*. Liver transplantation in the most severely ill cirrhotic patients: a multicenter study in acute-on-chronic liver failure grade 3. *J. Hepatol.* 2017; **67**: 708–15.
15 European Foundation for the Study of Chronic Liver Failure. CLIF-ACLF calculator. Available from URL: https://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf
16 Mezzano G, Juanola A, Cardenas A *et al*. Global burden of disease: acute-on-chronic liver failure, a systematic review and meta-analysis. *Gut*. 2022; **71**: 148–55.
17 Chetwood J, Sabih A-H, Chan K *et al*. IDDF2022-ABS-0190 Prevalence and outcomes of acute-on-chronic liver failure in Australia – a single-centre study. *Gut*. 2022; **71**: A93.
18 Bajaj JS, O'Leary JG, Reddy KR *et al*. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology*. 2014; **60**: 250–6.
19 Choudhury A, Jindal A, Maiwall R *et al*. Liver failure determines the outcome in patients of acute-on-chronic liver failure (ACLF): comparison of APASL ACLF research consortium (AARC) and CLIF-SOFA models. *Hepatol. Int.* 2017; **11**: 461–71.
20 Jayaraman T, Lee YY, Chan WK, Mahadeva S. Epidemiological differences of common liver conditions between Asia and the West. *JGH Open*. 2020; **4**: 332–9.
21 Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. *Gut*. 2017; **66**: 541–53.
22 Gustot T, Fernandez J, Garcia E *et al*. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. *Hepatology*. 2015; **62**: 243–52.
23 Kim JE, Sinn DH, Choi GS *et al*. Predictors and outcome of emergent liver transplantation for patients with acute-on-chronic liver failure. *Dig. Liver Dis.* 2021; **53**: 1004–10.
24 Belli LS, Duvoux C, Artzner T *et al*. Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: results of the ELITA/EF-CLIF collaborative study (ECLIS). *J. Hepatol.* 2021; **75**: 610–22.
25 Sundaram V, Jalan R, Wu T *et al*. Factors associated with survival of patients with severe acute-on-chronic liver failure before and after liver transplantation. *Gastroenterology*. 2019; **156**: 1381–1391.e3.
26 Sundaram V, Shah P, Wong RJ *et al*. Patients with acute on chronic liver failure grade 3 have greater 14-day waitlist mortality than status-1a patients. *Hepatology*. 2019; **70**: 334–45.
27 Agbim U, Sharma A, Maliakkal B *et al*. Outcomes of liver transplant recipients with acute-on-chronic liver failure based on EASL-CLIF consortium definition: a single-center study. *Transplant. Direct*. 2020; **6**: e544.
28 C.g. *Liver Transplantation in Patients With CirrHosis and Severe Acute-on-Chronic Liver Failure: iNdications and outComEs (CHANCE).* Available from URL: https://clinicaltrials.gov/ct2/show/NCT04613921
29 The Transplantation Society of Australia and New Zealand. *Clinical Guidelines for Organ Transplantation from Deceased Donors*, 2022.
30 Connor JP, Haber PS, Hall WD. Alcohol use disorders. *Lancet*. 2016; **387**: 988–98.
31 McDonough M, Baillie AJ, Clark PJ *et al*. Understanding and managing comorbidities for people with alcohol problems: polydrug use and dependence, co-occurring mental disorders, and physical comorbidities. *Med. J. Aust.* 2021; **215**: S28–32.
32 DiMartini A, Day N, Dew MA *et al*. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. *Liver Transpl.* 2006; **12**: 813–20.
33 Dew MA, DiMartini AF, Steel J *et al*. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. *Liver Transpl.* 2008; **14**: 159–72.
34 Mathurin P, Moreno C, Samuel D *et al*. Early liver transplantation for severe alcoholic hepatitis. *N. Engl. J. Med.* 2011; **365**: 1790–800.
35 Louvet A, Labreuche J, Moreno C *et al*. Early liver transplantation for severe alcohol-related hepatitis not responding to medical treatment: a prospective controlled study. *Lancet Gastroenterol. Hepatol.* 2022; **7**: 416–25.
36 Cotter TG, Sandıkçı B, Paul S *et al*. Liver transplantation for alcoholic hepatitis in the United States: excellent outcomes with profound temporal and geographic variation in frequency. *Am. J. Transplant.* 2021; **21**: 1039–55.
37 Im GY, Neuberger J. Debate on selection criteria for liver transplantation for alcoholic hepatitis: tighten or loosen? *Liver Transpl.* 2020; **26**: 916–21.
38 Marot A, Dubois M, Trépo E, Moreno C, Deltenre P. Liver transplantation for alcoholic hepatitis: a systematic review with meta-analysis. *PloS One*. 2018; **13**: e0190823.
39 Herrick-Reynolds KM, Punchhi G, Greenberg RS *et al*. Evaluation of early vs standard liver transplant for alcohol-associated liver disease. *JAMA Surg*. 2021; **156**: 1026–34.
40 Carrique L, Quance J, Tan A *et al*. Results of early transplantation for alcohol-related cirrhosis: integrated addiction treatment with low rate of relapse. *Gastroenterology*. 2021; **161**: 1896–1906.e2.