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REVIEW

Definition, diagnosis and epidemiology of acute-on-chronic liver failure

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Abstract

This narrative review addresses the definition of acute-on-chronic liver failure, a condition associated with high short-term mortality in patients with chronic liver disease and/or cirrhosis. We provide two major points of view: the East and the West perspective. Both definitions vary regarding the underlying patient population and organ failure(s) definition. Nevertheless, all the definitions have their clinical utility: from the core concept of having the "liver" as a *conditio* sine qua non, the syndrome cannot exist (Asian Pacific Association for the Study of the Liver); a data-driven, robust definition (European Association for the Study of the Liver); a bedside tool that can quickly identify patients at high risk of dying (North American Consortium for the Study of End-stage Liver Disease [NACSELD]). In each section, we provide the overall definitions, the criteria of organ failure(s), and some epidemiological data illustrating how these apply in each area of the world.

KEYWORDS
ACLF, definition, epidemiology

1 | BACKGROUND

In 1988, Sir Roger Williams stated that "patients may have established chronic liver disease and develop liver failure during intercurrent infections or variceal hemorrhage [...] with a slower course (encephalopathy developing within six months of onset), which has been termed late-onset hepatic failure (chronic/acute on chronic hepatocellular failure").[1] It was later in 1997 that the concept of acute-on-chronic liver failure (ACLF) was introduced back when describing hemodynamic changes after high-volume plasmapheresis,

Abbreviations: AARC, APASL ACLF Research Consortium; ACLF, acute-on-chronic liver failure; APACHE, Acute Physiology and Chronic Health Evaluation; APASL, Asian Pacific Association for the Study of the Liver; CANONIC, Consortium of Acute-on-Chronic Liver Failure in Cirrhosis; CATH-LIFE, Chinese Acute-on-Chronic Liver Failure; CLD, chronic liver disease; CLIF, Chronic LIver Failure; CMA, Chinese Medical Association; COSSH, Chinese Group on the Study of Severe Hepatitis; CPT, Child–Pugh-Turcotte; DAMPs, damage-associated molecular patterns; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HE, hepatic encephalopathy; INR, international normalized ratio; MARS, molecular adsorbent recirculating system; MELD, model for end-stage liver disease; NACSELD, North American Consortium for the Study of End-stage Liver Diseaseand the Study of End-stage Liver; PVT, Portal vein thrombosis; SAPS, Simplified Acute Physiology Score; SOFA, sequential organ failure assessment; TB, total bilirubin.

an early precursor of the molecular adsorbent recirculating system (MARS).[2] Later several papers highlighted the effect of MARS on ACLF,[3–5] until the Asian Pacific Association for the Study of the Liver (APASL) published the first consensus recommendations on the topic of ACLF.[6]

Considering that scope of the Journal is to be an "international forum", we provided a worldwide overview of the definitions and epidemiology of ACLF with special emphasis on three major defining groups: the Asian-Pacific,[6–8] the North-American[9,10] and the European[11] definitions. In 2014, the World Gastroenterology Organization proposed a working definition[12] with the following requirements "(1) The condition should be distinct from acute liver failure (ALF) and (2) distinguishable from "decompensated cirrhosis"; (3) pathophysiology should be defined; (4) specific clinical signs and laboratory or other tests that confirm the diagnosis and exclude other diseases should be stated; (5) a validated clinical scoring system to assess the severity of ACLF should be available". Unfortunately, the unifying principle did not prosper, and now we have several definitions to choose from. Each section will give an overview of the meaning of ACLF, what constitutes an organ failure, and the epidemiology of each of the three major prevailing definitions.

Key points

- Acute-on-chronic liver failure is a highly prevalent condition with high short-term mortality.
- The presence of cirrhosis sets apart the East and the West definitions.
- Liver failure is the organ with the highest variability in the ACLF definition.
- Each definition can be used clinically but depends on the aim of the study.

2 | THE ASIAN-PACIFIC PERSPECTIVE OF ACUTE ON CHRONIC LIVER FAILURE

2.1 | Definitions

As noted earlier, the APASL pioneered the first consensus to define ACLF in 2009, defining ACLF as hepatic failure manifesting as jaundice (total bilirubin (TB) ≥5 mg/dL) and coagulopathy (international normalized ratio (INR) >1.5 or prothrombin activity <40%) and complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.[6] The APASL ACLF Research Consortium (AARC), formed in 2012, updated the definition of ACLF in 2014 and 2019. The 2014 APASL definition emphasized the high 28-day mortality of ACLF patients and added bacterial infection to the list of acute insults.[7] Then, vascular liver diseases such as portal vein thrombosis (PVT), were added to the list of acute insults in 2019.[8] According to the APASL definition, hepatic failure was the only form of organ failure in the diagnostic criteria. Patients with underlying non-cirrhotic or cirrhotic chronic liver disease (CLD) who had an acute insult and later developed hepatic failure were labelled as having ACLF. On the contrary, patients with cirrhosis who presented with complications, including gastrointestinal bleeding, ascites, sepsis, hepatic encephalopathy (HE), and hepatorenal syndrome after an acute insult, were considered to have decompensated cirrhosis[6–8] without meeting the APASL definition of ACLF. Nevertheless, some regional data did include such patients. For example, Wang et al conducted a study including 1040 HBV patients with ACLF diagnosed by the APASL criteria, 15.9% (165/1040) patients were with prior decompensation.[13] Another study showed that in patients with ACLF of all aetiology (HBV accounted for 59%), 36.9% (254/689) of patients with single hepatic failure had decompensated cirrhosis.[14]

As the most populous country with endemic HBV infection, China defined ACLF as similar to the APASL but included decompensated cirrhosis. In 2006, the Chinese Medical Association (CMA) defined ACLF as developing hepatic failure over a short period in patients with chronic liver disease, with or without cirrhosis.[15] Later, in 2012, the CMA established detailed diagnostic criteria for hepatic failure: TB ≥10 mg/dL and INR ≥1.5, with extreme weakness and significant gastrointestinal symptoms, ascites, or HE.[16] Likewise, Japan was consistent with the APASL definition of ACLF, but they included patients with cirrhosis with a Child–Pugh-Turcotte score A/B[5–9] at baseline, not CPT class C (≥10).[17]

From 2009 to 2019, the APASL definition continuously focused on single hepatic failure for diagnosing ACLF in an early stage.[6–8] The APASL hypothesized that an acute hepatic insult leading to hepatic failure drove subsequent extrahepatic organ failure. In the APASL definition, extrahepatic organ failure was considered a complication of hepatic failure.[8] Mortality cumulatively increased with increased organ dysfunction or failure.[7] From the perspective of the APASL definition, the Western definitions[9,11] diagnosing ACLF with two organs or single extrahepatic failure (kidney failure) is considered too late and is contradictory to recognizing ACLF early.[8] In fact, studies on patients with chronic hepatitis B virus (HBV) have provided evidence to support that hepatic failure occurred before extrahepatic organ failure in HBV reactivation CLD patients supporting the APASL ACLF concept. In HBV-infected patients with the rs3129859*C and HLA-DRB1*12:02 alleles susceptible to developing ACLF,[18] HBV reactivation could induce HBV core-specific tumour necrosis factor (TNF)-α producing CD4+ T-cells rapid proliferation.[19] Large amounts of TNF-α lead to the necrosis of liver parenchymal cells.[20–22] As a critical histological feature of HBV-cirrhotic ACLF, submassive hepatic necrosis could trigger the release of many damage-associated molecular patterns (DAMPs).[23] Then, the innate immune response is upregulated, leading to systemic inflammation and, later, to extrahepatic organ failures.[24–27] Therefore, from the APASL ACLF perspective, choosing isolated hepatic failure as the diagnostic criteria could recognize ACLF early and exclude cirrhotic patients whose renal or circulation failures were driven by

either septic shock caused by sepsis or hypovolemic shock caused by oesophageal and gastric variceal bleeding.

2.2 | Diagnosis of ACLF in the East

While the definition of ACLF is relatively straightforward in Asia, the diagnostic criteria of "liver failure" are still controversial in the region and have up to five definitions: the APASL criteria (total bilirubin (TB) ≥5 mg/dL and INR ≥1.5),[8] the Japanese criteria (TB ≥12 mg/dL or INR >2.5),[17] the Chinese Group on the Study of Severe Hepatitis B (COSSH) (TB ≥12 mg/dL and INR ≥1.5),[27] the Chinese Medical Association (≥10 mg/dL and INR ≥1.5)[16] and the Chinese Acute-on-Chronic Liver Failure (CATCH-LIFE) criteria (TB >18 mg/dL or INR >2).[28,29] Despite this heterogeneity, a worldwide consensus exists to identify ACLF: a disease associated with 28-day liver transplant (LT)-free mortality greater than 15%.[8,9,11] The 28-day mortality of ACLF patients of AARC Grade I was 12.7%,[30] which fell short of the criterion of 15%, suggesting that the APASL cut-off may be too low to be specific for early mortality. Hence, some groups, such as CMA and COSSH, had chosen stricter criteria for hepatic failure. To obtain an evidence-based cut-off for reaching the threshold of 28-day LT-free mortality, the CATCH-LIFE study,[28,29] which investigated 3790 patients with cirrhosis and CLD, has acquired cut-off of TB (isolated TB >18 mg/dL)[28] for hepatic failure, and INR (isolated INR >2)[29] for coagulation failure using a multivariable Cox proportional hazards model.

What about other organ failures (OFs)? Some researchers in Asia use both hepatic and extrahepatic OFs and diagnostic criteria to rule in ACLF. For example, the COSSH group defines hepatic failure (TB ≥12 mg/dL and INR ≥1.5) or multiple organ failure using the EASL-CLIF criteria.[27] (Table 1).

2.3 | Epidemiology of ACLF in the East

The AARC cohort only included patients meeting the APASL-ACLF definition, making the prevalence of ACLF unavailable.[31] In contrast, 14 cohorts with different definitions provide a glimpse of the burden of ACLF in Asia: China (*N* = 7037),[14,29,32–38] Korea (*N* = 1470),[39] India (*N* = 1053),[40,41] Thailand (*N* = 706)[42] and Japan (*N* = 501).[43]

The prevalence of APASL-ACLF in hospitalized non-cirrhotic/cirrhotic patients from 3 cohorts[36,39,41] was 14.6% (713/4876) which ranged from 9.5% to 26.2%. The prevalence of patients using the other definitions which took single hepatic failure as diagnostic criteria of ACLF, including the Chinese[16] and the Japanese[17] criteria, were 19.8% (226/1144)[33,38] and 36.5% (183/501),[43] respectively. ACLF diagnostic criteria for multiple organ failure, including the EASL-CLIF, the NACSELD, and the COSSH, were also extensively applied in the region.

The prevalence of EASL-ACLF[34,35,39,40,42] and NACSELD-ACLF[39] in hospitalized patients with cirrhosis were 25.3% (1308/5167) and 7.5% (35/468), respectively. The prevalence of COSSH-ACLF in non-cirrhotic/cirrhotic CLD patients was 29.6% (391/1322).[32] In patients with APASL-ACLF from 5 cohorts (*N* = 3767), including the AARC cohort,[13,31,36,39,41] the most common etiologies were HBV (55.0%) and alcohol (29.3%). The aetiology differed from country to country, with alcohol being the most frequent underlying cause in Korea (82.1%, 78/95)[39] and India (70.4%, 247/351).[40,41] HBV was the most frequent aetiology in China (89.0%, 3469/3897)[14,29,32–38] and Thailand (38.2%, 131/343).[42] Among HBV-related ACLF patients, hepatic failure was the dominant organ failure, regardless of the definition used. In four Chinese cohorts (*N* = 2468) using different criteria for diagnosing HBV-related ACLF, the percentage of hepatic failure was 80.9%[13,36] in APASL-ACLF, 77.7%[34] in EASL-ACLF and 94.1% in COSSH-ACLF.[32] In EASL-CLIF-diagnosed ACLF patients with alcoholic aetiology, renal failure was the most common organ failure (70.2%, 379/540) (Table 2).[39,42] However, the APASL criteria would miss those patients because extrahepatic failure was not included in the definition.

3 | THE NORTH AMERICAN PERSPECTIVE OF ACUTE ON CHRONIC LIVER FAILURE: THE NORTH AMERICAN CONSORTIUM FOR END-STAGE LIVER DISEASE (NACSELD)

3.1 | The NACSELD Definition

The North American Consortium for End-Stage Liver Disease (NACSELD) is a consortium of tertiary-care hepatology centres in the USA and Canada that prospectively collected data on hospitalized patients with cirrhosis admitted with or developed an infection during their hospitalization.[44] Cirrhosis was defined by either (1) biopsy, (2) clinical evidence of decompensation or varices or (3) radiological evidence of liver nodularity and intra-abdominal varices in a patient with chronic liver disease. In contrast to other definitions,[8,11] the authors did not explicitly state whether the participant could have compensated disease at the time of enrolment; however, it is likely that this was the case since the mean value of the model for end-stage liver disease (MELD) at admission was 20 (standard deviation, 8). The main outcomes were death during admission or within 30 days of the first infection diagnosis; discharge to a facility, hospice, or home; liver transplantation.

In their initial publication of 207 patients (December 2010–December 2011), the authors described the epidemiology of infected and hospitalized North American patients with cirrhosis, including causes, organisms identified and antibiotic resistance patterns.[44] They found that most first infections were health-care associated (71%), then nosocomial (15%) and community-acquired (14%), being, urinary tract infections the most common infection (52%), followed by spontaneous bacterial peritonitis (23%) and spontaneous bacteremia (21%).

In 2014, the Consortium added the term "acute-on-chronic liver failure" and strived to simplify the EASL-CLIF definition mainly because it was "complex and also not specifically focused towards infections, which comprised a large percentage of [NACSELD] study

TABLE 1 Acute-on-chronic liver failure and organ failure criteria according to different scientific organizations or groups, chronologically ordered.

	Patients with decompensated cirrhosis included	ACLF criteria	Liver	Coagulation	Kidney	Brain	Circulation	Respiration
EAST								
APASL, 2009 & 2019[6,8]	NO	Presence of liver failure and coagulation failure	TB ≥5 mg/dL	INR≥1.5	N/A	Encephalopathy	N/A	N/A
CMA, 2013[16]	YES	Presence of liver failure and coagulation failure	TB ≥10	INR ≥1.5	N/A	N/A	N/A	N/A
Japan, 2018[17]	YES (only Child–Pugh score of 5–9)	Presence of liver failure and coagulation failure	TB ≥12 mg/dL	INR >2.5 or platelet count ≤20 000/mcl	Creatinine ≥2 mg/dL or hemodyalisis	West Haven III or IV	Use of dopamine or dobutamine	PaO2 to FiO2 ≤2000 o ratio of SpO2 to FiO2 ≤200
COSSH, 2018[32]	YES	Presence of 1* OF	TB ≥12 mg/dL	INR ≥1.5	Creatinine ≥2 mg/dL or RRT	West Haven III or IV	Use of inotropes	Mechanical ventilation or PaO2/FIO2 <200
CATCH-LIFE, 2021[28,29]	YES	Presence of 1* OF	TB >18 mg/dL	INR >2	Creatinine ≥2 mg/dL or RRT	West Haven III or IV	Use of inotropes	Mechanical ventilation or PaO2/FIO2 <200
WEST								
CANONIC, 2013[11]	YES	Presence of 1* OF	TB ≥12 mg/dL	INR ≥2.5	Creatinine ≥2 mg/dL or RRT	West Haven III or IV	Use of inotropes	Mechanical ventilation or PaO2/FIO2 <200
NACSELD, 2014[9]	YES	Presence of 2+ OF	N/A	N/A	RRT	West Haven III or IV	Use of inotropes	Mechanical ventilation

Note: (*) Requires (1) single kidney function failure; (2) single OF either of liver, blood coagulation, circulatory or respiratory function manifesting as a serum creatinine level of ≥1.5 mg/dL but <2 mg/dL, and/or grade I or II HE, (3) single cerebral function failure (From Moreau[11]).

Abbreviations: APASL, Asian Pacific Association for the Study of the Liver; CANONIC, Consortium of Acute-on-Chronic Liver Failure in Cirrhosis; CATH-LIFE, Chinese Acute-on-Chronic Liver Failure; CMA, Chinese Medical Association; COSSH, Chinese Group on the Study of Severe Hepatitis B; FiO2, fraction of inspired oxygen; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; PaO2, partial pressure arterial oxygen.

TABLE 2 Selected studies providing data on ACLF in the East and the West.

First author	Country/ Region	ACLF criteria	Cohort patient no.	ACLF prevalence	LT-free mortality (28-day/90-day) for ACLF patients	The percentage of cirrhosis in underlying CLD among ACLF	Aetiology (HBV/ alcohol/others)	Triggers (HBV-reactivation/alcohol/ infection)	The most common organ failure
Thanapirom[31]	Asia	APASL	1621	/	/	39%	18.8%/58.8%/22.4%	17%/51.3%/2%	Hepatic failure (79.8%)
Li[34]	China	EASL	890	33.7%	44.0%/50.0%	100%	100%/–/–	9%/10%/19.7%	Hepatic failure (77.7%)
Wu[32]	China	COSSH	1322	29.6%	46.5%/62.4%	77%	92.8%/4.9%/2.3%	/	Hepatic failure (94.1%)
Dong[38]	China	CMA	1144	19.8%	17.7%/26.1%	Liver	94.7%/1.8%/3.5%	/	/
Gao[36]	China	APASL	902	22.6%	/	21%	100%/–/–	77.3%/7.4%/12.9%	Hepatic failure (78.2%)
Xia[33]	China	CMA	857	/	/	53%	70.3%/6.5%/23.2%	/	/
Shi[35]	China	EASL	1454	14.4%	48.8%/62.2%	100%	59.3%/15.8%/24.9%	44.5% infection	Coagulation failure (48.8%)
Wang[13]	China	APASL	875	/	28.2%/41.7%	/	100%/–/–	/	Hepatic failure (83.8%)
Xu[14]	China	APASL	435	/	16.1%/31.4%	/	/	/	/
Kim[39]	Korea	APASL	1470	9.5%	/	100%	5.3%/82.1%/12.9%	5.3%/67.4%/8.4%	Hepatic failure (47.4%)
		EASL	1470	18.6%	/	100%	9.6%/73.6%/16.8%	2.0%/43.7%/19.8%	Renal failure (62.4%)
Gupta[40]	India	EASL	179	68.1%	55.7%/78.7%	100%	5.7%/64.8%/29.5%	6.6%/24.6%/36%	Hepatic failure (64.8%)
Bihari[41]	India	APASL	874	26.2%	/	/	7.4%/73.4%/19.2%	/	/
Maipang[42]	Thailand	EASL	706	48.6%	/	100%	38.2%/5.0%/56.8%	/	Renal failure (74.6%)
Nakayama[43]	Japan	Japanese	501	36.5%	–/49.7%	100%	3.3%/55.7%/41.0%	–/39.3%/21.9%	Hepatic failure (33.9%)
Cao[37]	China	EASL/NACSELD	468	29.3%	/	100%	65.0%/11.7%/23.3%	/	Hepatic failure (–)
Moreau[11]	Europe	EASL	1343	30.9%	32.8%/51.1%	100% cirrhosis	–/60.3%/–	–/24.5%/32.6%	Renal failure (55.8%)
Antunes[75]	Portugal	EASL	779	25.9%	/	100% cirrhosis	/	–/27.7%/64.4%	/
Piano[76]	Italy	EASL	466	25.3%	/	100% cirrhosis	/	/	Renal failure (64.0%)
Zaccherini[77]	Italy	EASL	516	32.0%	/	100% cirrhosis	–/18.6%/–	–/3.0%/53.0%	Renal failure (50.8%)
North America									
Hernaez[46]	USA	EASL	72316	26.40%	25.5%/40.0%	100% cirrhosis	–/28.2%/–	–/28.7%/14.5%	Renal failure (71.9%)
		NASCLED	72316	9.90%	33.0%/47.6%	100% cirrhosis	–/31.2%/–	–/32.9%/19.9%	Renal failure (75.3%)
Sundaram[78]	USA	EASL	100594	20.90%	/	100% cirrhosis	–/25.6%/–	/	Renal failure (62.7%)
Bajaj[9]	USA	NASCLED	507	25.00%	/	100% cirrhosis	Combined	/	Cerebral failure (55.7%)
O'Leary[10]	North America	NASCLED	2675	10%	/	100% cirrhosis	Combined	/	/
Rosenblatt[45]	USA	NASCLED	1523478	7.00%	/	100% cirrhosis	–/66.4%/–	/	/
Li[47]	USA	EASL	48547	21.00%	/	100% cirrhosis	–/43.7%/–	/	/
		NASCLED	48547	3.20%	/	100% cirrhosis		/	/

TABLE 3 Acute-on-chronic liver failure defined by the EASL-CLIF criteria.[11]

Definition	Definition
No ACLF	(1) Patients with acute decompensation of cirrhosis without organ failure (2) Patients with a single failure of the liver, coagulation, circulation, or respiration, who have a serum creatinine level <1.5 mg/dL and no hepatic encephalopathy (3) Patients with single cerebral failure who have a serum creatinine level <1.5 mg/dL
ACLF grade 1	(1) Patients with single kidney failure (2) Patients with single failure of the liver, coagulation, circulation, or respiration who have a serum creatinine level between 1.5 and 1.9 mg/dL and/or mild to moderate hepatic encephalopathy (3) Patients with single cerebral failure who have a serum creatinine level between 1.5 and 1.9 mg/dL
ACLF grade 2	Patients with 2 organ failures
ACLF grade 3	Patients with 3 organ failures or more

Note: The term 'patients' in this table refers to patients with acute decompensation of cirrhosis.

Abbreviation: ACLF, acute-on-chronic liver failure.

population".[9] The updated work included 18 hepatology referral centres across the USA and Canada and 436 patients with 30-day outcomes (Child-Pugh-Turcotte ≥7, 96% of the participants). They defined infection-related ACLF (I-ACLF) by the presence of two to four organ failures and was present in 25% of the cohort, with a 30-day mortality of 48.6% in the I-ACLF group compared to the 8.6% in the non-I-ACLF cohort.

Given that one of the major limitations of the external validity of the NACSELD Consortium was that it was only applicable to patients admitted with infection, the authors closed the gap when they published its validation study in non-infected patients using 14 centres across North America.[10] Out of 2675 patients, 1079 had an acute infection, and 1595 neither had an acute infection at admission nor developed one during their initial hospitalization (median, p25-p75, Child-Pugh-Turcotte 10, 8.0–11.0). From the prior I-ACLF, they renamed the score as NACSELD-ACLF using the same definition and was present in 10% of the cohort, with a 41% mortality at 30 days in the ACLF group compared to 7% in the non-ACLF group.

So overall, the NACSELD experience evolved from understanding the epidemiology and natural history of infected patients with cirrhosis in North America to a more comprehensive definition to identify "at bedside" critically sick patients with cirrhosis.

3.2 | Diagnosis of organ failure in NACSELD

To define ACLF, the NASCELD Consortium used four organ failures (OFs): brain, respiratory, circulatory, and kidney failures. In contrast to other definitions, the authors did not include "liver-specific" laboratory values such as INR or bilirubin for two reasons: "they were difficult to translate into simple criteria and, in the multivariable analyses using INR and bilirubin individually in this group did not predict outcomes"[9] (Table 1). In the setting of decompensated cirrhosis population with a 96% prevalence of Child-Pugh-Turcotte ≥7 on admission, the authors hypothesized that "liver failure", was a susceptibility marker of infection rather than a prognostic factor as compared to non-hepatic organ failure.[9]

Brain failure was defined by the presence of hepatic encephalopathy grade III or IV by West Haven Criteria; circulatory failure ("shock"), was defined by a mean arterial pressure (MAP) <60 mm Hg or a reduction of 40 mmHg in systolic blood pressure [from baseline] despite adequate fluid resuscitation and cardiac output; the need for mechanical ventilation defined the presence of respiratory failure and, finally, kidney failure was present when the patients needed dialysis or other forms of renal replacement therapy.

The kidney failure definition differs from other consortia since it does not include serum creatinine values.[7,11] In NACSELD, the criteria for dialysis initiation were centre-specific without uniformity in its initiation. However, the authors felt that dialysis was, rather than a marker of prognosis reflecting severe kidney injury, a surrogate of good prognosis since "this intervention may only be offered to individuals thought likely to recover from the infection and go on to liver transplant".[9]

3.3 | Epidemiology of ACLF using the NACSELD criteria

NACSELD-ACLF was present in 10% of the original total cohort (infected and non-infected participants with cirrhosis)[10] (Table 2). In the USA, other cohorts had similar prevalence estimates using such criteria: 7.0% using the National Inpatient Sample cohort,[45] 9.8% in the Veterans Administration population,[46] or 15.3% in the United Network for Organ Sharing (UNOS) database (2016–2020).[47] Cao et al in China found a 7.4% prevalence of NACSELD-ACLF in 468 patients with decompensated cirrhosis.[37]

While the NACSELD-ACLF expanded knowledge in non-infected patients, published granular data are only available in the infected cohort.[9] The most common organ failure noted in the I-ACLF cohort was hepatic encephalopathy (55.7%), followed by shock (17.5%), mechanical ventilation (15.8%) and renal replacement therapy (15.1%).[9] In contrast, the VA population had two OFs in 7.9%, 1.7% three OFs, 4 OFs were present in 0.3%,[46] which is also consistent with figures observed in the National Inpatient Sample study (5.1% two OF, 1.6% three OF, and 0.3% four OF).[45] The difference in the estimates between the I-ACLF and the other American cohorts is likely due to the use of the general population rather than the tertiary care liver transplant centres in the USA.

The presence of defining OF was as follows in the I-ACLF cohort: 37.3% experienced a single organ failure, 10.4% had two organ failures, 10% had three organ failures and 4% had all four organ failures.[9]

Except for Cao et al, the studies validating NACSELD OF criteria provided survival rates by the presence of each organ failure. In China, circulatory (61.7%) and cerebral (60.0%) were the most common OF, followed by respiratory (45%) and kidney failure (28.3%).[37]

The 30% mortality was 41% in the NACSELD-ACLF cohort (vs. 7% in the non-ACLF group).[10] Whether patients were infected or not, the 30-day mortality varied: 16%–38% for two OFs, 35%–58% for three OFs, and 100%–76% for four OFs in the uninfected vs. infected participants (2018). More conservative estimates were seen in the VA population, with a 30-day mortality rate of 22.3%, 31.9% and 41% for the presence of two, three or four OFs, respectively.[46] The National Inpatient Sample study had estimates between the NACSELD 2018 analysis and the VA ones[45] (Table 2).

4 | THE EUROPEAN PERSPECTIVE OF ACUTE ON CHRONIC LIVER FAILURE: THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)-CHRONIC LIVER FAILURE (CLIF) CONSORTIUM

4.1 | The EASL-CLIF definition

The EASL-CLIF Consortium performed the Consortium Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study, a prospective observational study aiming to develop a scientifically-sound definition of ACLF. Of note, the European investigators considered that criteria defining ACLF should be established in patients with cirrhosis, an assumption distinguishing European investigators from Asian-Pacific investigators who considered that ACLF might develop in patients without cirrhosis. The CANONIC study was performed in a cohort of 1343 European patients from 29 university hospitals who were hospitalized non-electively for acute decompensation of cirrhosis as defined by acute development of large ascites, hepatic encephalopathy, gastrointestinal haemorrhage, bacterial infection or any combination of these.[11] Upon enrolment, it was determined whether organ failure was present or not. Patients who did not have organ failure at enrolment had regular follow-ups to detect the development of organ failure. Diagnostic criteria for organ failures were defined before the start of the study according to the CLIF-sequential organ failure assessment (SOFA) score, a set of strict criteria defined explicitly for this study. Based on the results of this study, the following EASL-CLIF definition was developed: ACLF is defined as patients with acute decompensation of cirrhosis with concomitant organ failure(s) and a high short-term mortality rate. The presence of kidney failure, ≥2 organ failures, the coexistence of any other organ failure and kidney dysfunction and/or mild to moderate hepatic encephalopathy were significant risk factors for 28-day mortality. Based on this observation, four groups were defined, ranging from no ACLF to ACLF grade 3 (Tables 1 and 3). Ninety-day mortality risk increased significantly with increasing grade of ACLF, ranging from 41% for ACLF grade 1 to 78% for ACLF grade 3. Some important observations were made in this study. *First*, a systemic inflammatory response was observed in patients with ACLF as compared to patients with acute decompensation of cirrhosis without organ failure. *Second*, 43% of patients with ACLF at enrolment did not have any identifiable potential precipitating event of ACLF. *Third*, among patients who were identified as having ACLF in the CANONIC study, 31% had no previous episode of acute decompensation and the disease course was especially severe in these patients. Finally, the most prevalent organ failure was the kidney for ACLF grade 1 and the liver for ACLF grade 2. For ACLF grade 3, the prevalence of all organ failures was high, except for the lungs.

4.2 | Organ failure using the EASL-CLIF criteria

Since the presence of organ failure is a key element of ACLF, the development of the CLIF-SOFA score and its background deserve some elaboration. The SOFA score, which served as a basis for the CLIF-SOFA score, was developed in 1994 by consensus by a group of critical care physicians,[48] based on three principles[1]: organ failures should be regarded as a range of degrees of severity, rather than just the presence or absence of failure,[2] the severity of organ dysfunction is a dynamic process which may vary with time and should be reassessed to follow disease evolution,[3] the definition of organ failure should be based on simple, widely available variables. The SOFA score consists of scores from six organ systems, graded from 0 to 4 according to the degree of dysfunction/failure, namely respiration as assessed by PaO2/FiO2 ratio, coagulation (platelet count), liver (bilirubin concentration), cardiovascular (mean arterial pressure or the use of vasoconstrictors), central nervous system (Glasgow Coma Score) and renal function (creatinine concentration of urine output). The SOFA score was originally developed to describe morbidity, but it appeared to also correlate well with mortality in critically ill patients. The CLIF-SOFA score (Table 4), was specifically developed for the EFClif study by the authors, modifying the SOFA score for specific features present in patients with cirrhosis based on their expertise. The definition and grading of failure of respiratory function, liver, cardiovascular function, and kidney are identical in CLIF-SOFA and SOFA scores, but coagulation dysfunction/ failure in the CLIF-SOFA score is based on INR rather than platelet count, which is affected by the presence of portal hypertension and associated splenomegaly in patients with acute decompensation of cirrhosis. INR is widely available and is included in several models to predict survival in patients with cirrhosis, such as the CPT score,[49] model for end-stage liver disease (MELD) score[50] and MELD-sodium score.[51] However, the INR was designed to standardize the anticoagulation effect of warfarin and is therefore influenced by anticoagulants, which may hamper its use in the CLIF-SOFA score. The cerebral dysfunction/failure is graded according to the West Haven score instead of the Glasgow coma score.[11] A limitation of the West Haven score is that it is based on a subjective assessment obtained by physical examination and, as a result, it is heavily operator dependent. More accurate classifications have been developed for

TABLE 4 The CLIF-SOFA score.[11]

Organ/System	0	1	2	3	4
Liver (bilirubin, mg/dl)	<1.2	≥1.2 to <2.0	≥2.0 to <6.0	≥6.0 to <12.0	**≥12.0**
Kidney (creatinine, mg/dl)	<1.2	≥1.2 to <2.0	**≥2.0 to <3.5 Or use of renal replacement therapy**	**≥3.5 to <5.0 Or use of renal replacement therapy**	**≥5.0 Or use of renal replacement therapy**
Cerebral (HE grade)	No HE	I	II	III	IV
Coagulation (INR)	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	**≥2.5 or platelet count ≤ 20×10^9/L**
Circulation (MAP, mmHg)	≥70	<70	**Dopamine ≤5 or dobutamine or terlipressin**	**Dopamine >5 or E ≤0.1 or NE ≤0.1**	**Dopamine >15 or E >0.1 or NE >0.1**
Lungs					
PaO2/FiO2 or	>400	>300 to ≤400	>200 to ≤300	**>100 to ≤200**	**≤100**
SpO2/FiO2	>512	>357 to ≤512	>214 to ≤357	**>89 to ≤214**	**≤89**

Note: The CLIF-SOFA score includes subscores per organ/system, ranging from 0 to 4 for the following organs/systems: liver, kidney, cerebrum, coagulation, circulation and lungs. Higher scores indicate more severe organ/ system dysfunction. The sum of the individual organ/system scores provides information on the overall disease severity in an individual patient. Texts in bold indicate the diagnostic criteria of organ failures.

Abbreviations: E, epinephrine; FiO2, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, international normalized ratio; NE, norepinephrine; PaO2, partial pressure of arterial oxygen; SpO2, pulse oximetric saturation.

hepatic encephalopathy, such as the hepatic encephalopathy scoring algorithm (HESA),[3] the clinical hepatic encephalopathy staging tool (CHESS),[52] the hepatic encephalopathy staging tool (HEST)[53] and the hepatic encephalopathy grading instrument (HEGI),[54] but these classifications are only used in clinical trials so far. The decision to use the SOFA score instead of the acute physiology and chronic health evaluation (APACHE) II system to develop a definition of ACLF in the CANONIC study seems appropriate since the prognostic accuracy for mortality was significantly superior for SOFA as compared to APACHE II system[55,56] or simplified acute physiology score (SAPS) II[57] in acutely ill patients with cirrhosis. In the APACHE II system, cardiovascular, respiratory, kidney and brain function biomarkers are included, but liver failure is not explicitly included, except for a history of severe organ failure, including cirrhosis. The SAPS score includes cardiovascular, brain, respiratory, liver and kidney function biomarkers, but coagulation function is lacking.

Contrary to what the term ACLF may suggest, the presence of liver failure (defined by highly elevated bilirubin levels, i.e. ≥12 mg/dL) is not a prerequisite for ACLF according to the EASL-CLIF definition. For example, European patients with isolated liver failure, a serum creatinine level <1.5 mg/dL, and no hepatic encephalopathy are considered not to have ACLF according to the EASL-CLIF criteria.[11] Conversely, patients with isolated kidney failure (and therefore no liver failure) are considered as having ACLF. EASL-CLIF criteria succeed in identifying patients at high risk of mortality and, therefore, may be useful tools for making clinical decisions. Suppose the presence of liver failure is not a necessary condition to define ACLF according to European criteria. In that case, this does not mean impaired liver function does not contribute to poor outcomes in patients with acutely decompensated cirrhosis. Recently, published results of a prospective observational study (called ACLARA study) conducted in 1274 Latin American patients non-electively hospitalized for acutely decompensated cirrhosis have shown that lower baseline albumin levels (considered here as markers of perturbed liver function) were independently associated with higher transplant-free mortality.[58] In a retrospective study on ACLF in patients with compensated cirrhosis, it was observed that mortality rates for patients with total bilirubin <5 mg/dL were 26.4% at 28 days and 39.4% at 90 days, respectively, as compared to 63.7% and 76.3% in patients with bilirubin ≥5 mg/dL.[59] It is well recognized that acute decompensation of cirrhosis is a very heterogeneous condition with two different pathophysiological mechanisms involved: systemic inflammation and portal hypertension.[60] Future studies should be aimed at studying the pathophysiology of individual organ failures and their interaction in ACLF and at harmonizing the definitions of organ failures and those applied for therapeutic strategies.

4.3 | Applicability of a uniform ACLF definition in research and in clinical practice

The benefit of a uniform and evidence-based definition is that it aids in prognostication and enables research in the field of improved understanding of pathophysiology and therapeutic interventions aimed at preventing or treating ACLF and epidemiology. The premise that organ dysfunction is a dynamic process that may vary with time and should be reassessed to follow disease evolution also holds for patients with ACLF. Gustot et al[61] showed that ACLF resolved or improved in 49%, had a fluctuating course in 30%, and deteriorated in 20% of patients with ACLF, determined at the last available assessment in the first 28 days after diagnosis, before death, liver

transplantation or discharge from hospital. After 3–7 days, 81% of patients had reached their final ACLF grade, and accurate prediction of 28 and 90 days mortality was possible then. This may support treatment decisions in clinical practice, including decisions on the futility of intensive care support in patients with ACLF.[62] Another important message of this study was that critically ill patients with ACLF should receive appropriate full support during the first days of hospitalization because of potential reversibility, resulting in relatively low mortality (35%–40%) in the first week. The mortality rate in critically ill patients with persistent severe ACLF grade 3 beyond the first week of intensive care support was found to be very high, potentially due to limited regenerative capacity. Results obtained from the CANONIC cohort have been used to develop different scores. *First*, the CLIF Consortium (CLIF-C) organ failure score was developed to assess the six major organ systems more simply than the CLIF-SOFA score. Indeed, the CLIF-C organ failure score assessed each organ system using a 3-point scale instead of the 5-point scale for the CLIF-SOFA score. Second, a prognostic score calculator was developed for patients with ACLF using data from the CANONIC study.[63] The CLIF-C organ failure scores, age, and white blood cell count, all independent predictors of mortality, were combined to develop the CLIF Consortium ACLF score, a prognostic score for ACLF. Age and white blood cell count have not been included in the original SOFA or CLIF-SOFA scores, as opposed to the APACHE II and SAPS scores. The CLIF-C ACLF score was shown to have significantly higher accuracy in predicting mortality, as reflected in the concordance index (C-index) ranging between 0.76 and 0.71 for different time points, than the conventional scores MELD (C-indices 0.64–0.68), MELD-Na (C-indices 0.64–0.68) and CPT (C-indices 0.64–0.67) in the derivation cohort. These findings were validated in an external independent cohort. Importantly, the performance of the CLIF-C ACLF score computed during follow-up on day 2, 3–7 days and 8–15 days after diagnosis of ACLF in predicting the 28-day mortality was even better than at diagnosis, which makes this score relevant in clinical practice as a prognostic tool to follow the disease evolution over time.

The utility of this evidence-based definition of ACLF in daily practice for guiding treatment decisions of individual organ dysfunction/failure is hampered by discrepancies between the CLIF-SOFA grading systems and criteria currently in use for individual organ function impairment. Regarding renal impairment, the presence of kidney dysfunction in the CLIF-SOFA score is defined as creatinine concentration ≥1.2 to <2.0 mg/dL, and renal failure as a creatinine concentration ≥2.0 mg/dL. It has long been recognized that serum creatinine concentration in patients with cirrhosis may underestimate the glomerular filtration rate due to low creatinine production secondary to reduced muscle mass. Moreover, a spot serum creatinine concentration does not allow to discriminate between the presence of chronic kidney disease if previous creatinine concentrations are not considered. Finally, according to the new International Ascites Club criteria, the diagnosis of acute kidney injury in patients with cirrhosis is based on an absolute increase in serum creatinine of ≥0.3 mg/dL (26.4 μmoL/L) in less than 2 days or by a ≥ 50% increase in serum creatinine concentration from baseline within 3 months in 1 week.[64] Based on absolute serum creatinine concentration, the staging system of renal dysfunction/failure in CLIF-SOFA score does not allow for selecting appropriate therapeutic interventions in daily practice[65] and strict follow-up of the dynamics in creatinine concentration over time is required.

4.4 | Epidemiology of ACLF according to EASL-CLIF definition

The prevalence of ACLF, according to the EASL-CLIF definition, was 30% in the CANONIC study, in patients hospitalized non-electively with acute decompensation of cirrhosis, supported recently by a meta-analysis.[66] Kidney failure was the most frequent organ failure in 55% of cases with ACLF, and alcoholic cirrhosis was the most frequent underlying liver disease in 49% of cases[11] (Table 2). In a retrospective study in Swedish patients with cirrhosis requiring hospitalization for a severe bacterial infection, ACLF was present in 24%. Also, in this population, alcoholic cirrhosis was the most frequent underlying liver disease, and kidney failure was the most frequent organ failure in patients with ACLF.[67] In a prospective Chinese cohort of hospitalized patients with hepatitis B infection and AD, 33.7% of patients were diagnosed with ACLF, with liver failure being the most frequent organ failure in 77% of patients with ACLF in this cohort. Renal failure was present in only 14% of cases.[34] In the PREDICT study, three different clinical courses of AD were identified, that is, stable decompensated cirrhosis (not requiring hospital readmission <3 months), unstable decompensated cirrhosis (requiring hospital readmission <3 months without developing ACLF) and pre-ACLF (ACLF development <3 months), each with a clearly different prognosis and with portal hypertension and systemic inflammation as major underlying pathophysiological mechanisms.[60] For clinical practice and future research, it would be highly relevant to define which patients with cirrhosis are at elevated risk of ACLF development or mortality with variables available a priori. The CLIF-C AD score, based on age, serum sodium, white-cell count, creatinine and INR, was shown to be more accurate than the CPT, MELD and MELD-Na score in predicting 3- and 12-month mortality in hospitalized cirrhotic patients without ACLF. The CLIF C-AD score can be recalculated to follow the disease course with C-indices ranging between 0.72 and 0.77.[68]

5 | CONCLUSIONS

The core concept of ACLF identifies a group of patients at high risk of mortality. In this narrative review, we showed several regional differences in the definition of the concept (presence or absence of cirrhosis), the number, and the definitions of OFs. Regardless, since its conceptual development in the late 1980s, today, powerful studies provide light on this condition's epidemiology and natural history.

There are still some areas of unmet research needs, for example, to understand the natural history/prognosis of ACLF based on the

TABLE 5 Strengths and limitations of the Asian-Pacific, North-American and European Definitions.

	Strengths	Limitations	Main points and deviations?
Asian Pacific Association for the Study of the Liver (APASL)	1. A set of liver-initiated organ failure criteria provides more chances for early intervention to slow the progress or reverse the liver failure and improve survival[79] 2. A simple bedside tool which is easy for a quick diagnosis[79]	1. APASL definition did not investigate the difference between cirrhotic and non-cirrhotic patients and used the same criteria for these different populations. ACLF diagnosed by the definition was heterogeneous and had various outcomes 2. The most common form of ACLF in the Western area occurs in patients with decompensated cirrhosis and bacterial infections or active alcoholism, but these patients are not included in the APASL definition[24] 3. Renal failure was the most common type of organ failure in patients with ACLF and active alcoholism, but it was missing in APASL definition 4. The APASL concept that decompensated cirrhosis represents a terminal phase of the disease is not the experience of European centres[24]	1. APASL definition relies on the presence of liver failure; their simple bedside tool provides more chances for early intervention to prevent further liver damage 2. For further improvement a. Since non-cirrhotic and cirrhotic patients have heterogeneous outcomes, it is necessary to develop separate evidence-based liver-initiated organ failure criteria suitable for each of them b. The criteria should be applicable to a population including patients with previous decompensation and patients with bacterial infection
North American Consortium for End-Stage Liver Disease (NACSELD)	1. It provides an easy, bedside tool without the need for calculators to assess critically sick patients with acute-on-chronic liver failure[9,10] 2. Those meeting 2+ organ failure criteria are at very high risk of short-term mortality. It can identify the futility of liver transplant[10]	1. While it is highly specific to detect very high mortality risk ACLF, it is less sensitive to detect early grades of ACLF where intervention/triage might be possible[46] 2. The definition excludes coagulation and liver failure defined by other societies making comparisons more challenging 3. Derived from a multicenter U.S. cohort with higher proportions of alcohol-associated cirrhosis (45%), and the presence of diabetes mellitus (34%)[9,10] 4. Validation outside of the USA is limited to a few cohorts[37]	1. Those patients not meeting the NACSELD ACLF criteria should still be considered at high mortality risk 2. The concept of futility may not apply to all grades of ACLF and future work should include other organ failures to capture early stages of ACLF 3. Given the sharp rise of alcohol-associated hepatitis in the U.S, future studies should be aimed at assessing the association between different precipitating factors and prognosis in ACLF
European Association for the Study of the Liver-Chronic Liver Failure consortium (EASL-CLIF)	1. Definition of ACLF and its grading of severity is derived from a prospective observational study specifically designed to develop a scientifically-sound definition of ACLF 2. Definition of organ failures is a modification of the widely applied SOFA-score 3. Prognostic score calculators for patients with AD at risk of ACLF and with ACLF are available for clinical use at bedside	1. The cerebral dysfunction/failure according to the European ACLF criteria is graded according to the West Haven score, which is based on a subjective assessment obtained by physical examination and, therefore, operator dependent 2. ACLF criteria have been developed in hospitalized patients with acute decompensation of cirrhosis. Heterogeneity may exist in the criteria for hospitalization, which may affect the generalizability of the criteria 3. Discrepancies exist between the CLIF-SOFA grading system and criteria currently in use for therapeutic strategies in individual organ function impairment 4. The term 'ACLF' may be confusing, since ACLF may exist in the absence of liver failure according to the strict organ failure criteria	1. ACLF criteria are applicable to patients with acute decompensation of cirrhosis, not to non-cirrhotic patients 2. Presence of strictly defined liver failure is not a prerequisite for the presence of ACLF 3. The impact of pre-existing organ impairments/failures on prognostication and therapeutic strategies should be investigated in future studies 4. Future studies should be aimed at harmonizing the definitions of organ failures and those applied to therapeutic strategies

underlying chronic liver disease in the same areas of the globe; or the effect on the overall prognosis of ACLF by the type of trigger/organ failure.

Prior analyses showed infections, compared to other factors, were the triggers most negatively associated with short-term mortality.[46,69,70] Furthermore, fungal infections were associated with a worse prognosis than bacterial ones,[71,72] potentially suggesting that prophylactic fungal therapy might be a tool to improve outcomes in patients with ACLF or, at least, if they had some prior risk factors (e.g. exposure to antibiotics during the index hospitalization).

Similarly, the type of underlying chronic liver disease can also influence mortality, probably due to extrahepatic factors. For example, Sundaram et al, using the United Network for Organ Sharing registry, showed that NAFLD-ACLF had a greater waitlist mortality rate relative to alcohol-associated ACLF or HCV-related ACLF.[73] The CANONIC study showed that the type of organ failure mattered: those participants "with single liver failure (or any other 'non-kidney organ failure) had a low risk of death unless they also had kidney dysfunction and/or mild to moderate hepatic encephalopathy".[11] In the setting of liver transplant candidates, recovery from circulatory, brain or respiratory failure(s) was also good prognostic factor for post-liver transplant mortality.[74]

How can we use all these definitions? Each definition has pros and cons (Table 5). For the researcher, the European definition provides a much better opportunity to articulate different hypotheses due to the presence of more granular data in a well-defined group of patients, namely those with acute decompensation of cirrhosis. In contrast, if the reader is looking at the easiest concept to use to identify patients at higher risks of poor outcomes quickly, then the NACSELD definition provides such an approach. The APASL definition can also be incorporated in any additional analyses of either definition to assess the presence of "liver failure" as a core concept in the syndrome definition. Applying disease-specific definitions could be helpful as well. For example, *for chronic hepatitis B*, we showed a better characterization could be the Chinese Group on the Study of Severe Hepatitis B (COSSH) definition. As discussed in our paper, the main conflict between the EASL/AASLD and APASL definitions is what qualifies as 'chronic'. We developed this newer definition in a cohort of 391 patients that met the initial APASL criteria (hospitalized at least 1 day with severe liver injury with total bilirubin ≥5 mg/dL, and INR ≥1.5) from chronic hepatitis B, or acute decompensation of cirrhosis. Using the EASL-CLIF definition, we found that HBV-infected patients with chronic liver disease and a TB ≥12 mg/dL and an INR ≥1.5 have higher short-term mortality, which should be included in the ACLF definition and identified approximately 20% more patients with ACLF who can receive earlier clinically intensive management. Therefore, for CHB, the clinician could use the COSSH and/or the EASL-CLIF definition, considering the latter might be less sensitive to detecting ACLF. COSSH criteria could cover different types OFs for HBV-related ACLF patients. It not only included liver failure patients by more strict total bilirubin level but also could identify extrahepatic OF patients whose liver damage had not reached OF level. For HBV-related cirrhotic/without cirrhotic patients, COSSH might be a better ACLF diagnostic criterion than APASL.

Regarding the use of APASL in Europe, considering the differences in the phenotypic definition of the metabolic syndrome, diet/food-host interaction, the use of APASL in Western populations is probably not indicated. Nevertheless, data using a cohort of U.S. veterans showed that both definitions (EASL-CLIF and APASL) identified a group with high short-term mortality, with a higher proportion identified with APASAL of liver-specific injury, compared to non-hepatotropic causes using EASL-CLIF.[59] We, therefore, conclude that, except for CHB, EASL-CLIF is still applicable worldwide[66] and that all definitions highlight patients with higher short-term mortality risk.

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CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Williams R. Management of acute liver failure. *Postgrad Med J*. 1988;64:769-771.
2. Clemmesen JO, Larsen FS, Ejlersen E, Schiodt FV, Ott P, Hansen BA. Haemodynamic changes after high-volume plasmapheresis in patients with chronic and acute liver failure. *Eur J Gastroenterol Hepatol*. 1997;9:55-60.
3. Hassanein T, Oliver D, Stange J, Steiner C. Albumin dialysis in cirrhosis with superimposed acute liver injury: possible impact of albumin dialysis on hospitalization costs. *Liver Int*. 2003;23(Suppl 3):61-65.
4. Khuroo MS, Khuroo MS, Farahat KLC. Molecular adsorbent recirculating system for acute and acute-on-chronic liver failure: a meta-analysis. *Liver Transpl*. 2004;10:1099-1106.
5. Choi JY, Bae SH, Yoon SK, et al. Preconditioning by extracorporeal liver support (MARS) of patients with cirrhosis and severe liver failure evaluated for living donor liver transplantation—a pilot study. *Liver Int*. 2005;25:740-745.
6. Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int*. 2009;3:269-282.
7. Sarin SK, Kedarisetty CK, Abbas Z, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. *Hepatol Int*. 2014;8:453-471.

8. 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;13:353-390.
9. 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;60:250-256.
10. 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;67:2367-2374.
11. 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;144:1426-1429.
12. Jalan R, Yurdaydin C, Bajaj JS, et al. Toward an improved definition of acute-on-chronic liver failure. *Gastroenterology*. 2014;147:4-10.
13. Wang H, Tong J, Xu X, et al. Reversibility of acute-on-chronic liver failure syndrome in hepatitis B virus-infected patients with and without prior decompensation. *J Viral Hepat*. 2022;29:890-898.
14. Xu M, Kong M, Yu P, et al. Acute-on-chronic liver failure defined by Asian Pacific Association for the Study of the liver should include decompensated cirrhosis. *Front Med (Lausanne)*. 2021;8:750061.
15. Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Severe Liver Diseases and Artificial Liver Group, Chinese Society of Hepatology. Diagnostic and treatment guidelines for liver failure. *Zhonghua Gan Zang Bing Za Zhi*. 2006;14:643-646.
16. Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Severe Liver Diseases and Artificial Liver Group, Chinese Society of Hepatology. Diagnostic and treatment guidelines for liver failure. *Zhonghua Gan Zang Bing Za Zhi*. 2012;2013(21):177-183.
17. Mochida S, Nakayama N, Ido A, et al. Proposed diagnostic criteria for acute-on-chronic liver failure in Japan. *Hepatol Res*. 2018;48:219-224.
18. Tan W, Xia J, Dan Y, et al. Genome-wide association study identi fi es HLA-DR variants conferring risk of HBV-related acute-on-chronic liver failure. *Gut*. 2018;67:757-766.
19. Wang H, Luo H, Wan X, et al. TNF-alpha/IFN-gamma profile of HBV-specific CD4 T cells is associated with liver damage and viral clearance in chronic HBV infection. *J Hepatol*. 2020;72:45-56.
20. Karki R, Sharma BR, Tuladhar S, et al. Synergism of TNF-alpha and IFN-gamma triggers inflammatory cell death, tissue damage, and mortality in SARS-CoV-2 infection and cytokine shock syndromes. *Cell*. 2021;184:149-168.e17.
21. Newton K, Manning G. Necroptosis and inflammation. *Annu Rev Biochem*. 2016;85:743-763.
22. Schwabe RF, Luedde T. Apoptosis and necroptosis in the liver: a matter of life and death. *Nat Rev Gastroenterol Hepatol*. 2018;15:738-752.
23. Li H, Xia Q, Zeng B, et al. Submassive hepatic necrosis distinguishes HBV-associated acute on chronic liver failure from cirrhotic patients with acute decompensation. *J Hepatol*. 2015;63:50-59.
24. Arroyo V, Moreau R, Kamath PS, et al. Acute-on-chronic liver failure in cirrhosis. *Nat Rev Dis Primers*. 2016;2:16041.
25. Sarin SK, Choudhury A. Management of acute-on-chronic liver failure: an algorithmic approach. *Hepatol Int*. 2018;12:402-416.
26. Khanam A, Kottilil S. Abnormal innate immunity in acute-on-chronic liver failure: immunotargets for therapeutics. *Front Immunol*. 2020;11:2013.
27. Li J, Liang X, Jiang J, et al. PBMC transcriptomics identifies immune-metabolism disorder during the development of HBV-ACLF. *Gut*. 2022;71:163-175.
28. Qiao L, Tan W, Wang X, et al. Different effects of total bilirubin on 90-day mortality in hospitalized patients with cirrhosis and advanced fibrosis: a quantitative analysis. *Front Med (Lausanne)*. 2021;8:704452.
29. Wang Y, Dong F, Sun S, et al. Increased INR values predict accelerating deterioration and high short-term mortality among patients hospitalized with cirrhosis or advanced fibrosis. *Front Med (Lausanne)*. 2021;8:762291.
30. 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;11:461-471.
31. Thanapirom K, Teerasarntipan T, Treeprasertsuk S, et al. Impact of compensated cirrhosis on survival in patients with acute-on-chronic liver failure. *Hepatol Int*. 2022;16:171-182.
32. Wu T, Li J, Shao L, et al. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. *Gut*. 2018;67:2181-2191.
33. Xia Q, Dai X, Zhang Y, et al. A modified MELD model for Chinese pre-ACLF and ACLF patients and it reveals poor prognosis in pre-ACLF patients. *PLoS One*. 2013;8:e64379.
34. Li H, Chen L, Zhang N, et al. Characteristics, diagnosis and prognosis of acute-on-chronic liver failure in cirrhosis associated to hepatitis B. *Sci Rep*. 2016;6:25487.
35. Shi Y, Shu Z, Sun W, et al. Risk stratification of decompensated cirrhosis patients by Chronic Liver Failure Consortium scores: classification and regression tree analysis. *Hepatol Res*. 2017;47:328-337.
36. Gao F, Zhang Q, Liu Y, et al. Nomogram prediction of individual prognosis of patients with acute-on-chronic hepatitis B liver failure. *Dig Liver Dis*. 2019;51:425-433.
37. Cao Z, Liu Y, Cai M, et al. The use of NACSELD and EASL-CLIF classification systems of ACLF in the prediction of prognosis in hospitalized patients with cirrhosis. *Am J Gastroenterol*. 2020;115:2026-2035.
38. Dong FC, Tan WT, Wang XB, et al. The neutrophil-to-lymphocyte ratio represents a systemic inflammation marker and reflects the relationship with 90-day mortality in non-cirrhotic chronic severe hepatitis. *J Dig Dis*. 2022;23:587-596.
39. Kim TY, Song DS, Kim HY, et al. Characteristics and discrepancies in acute-on-chronic liver failure: need for a unified definition. *PLoS One*. 2016;11:e0146745.
40. Gupta T, Dhiman RK, Rathi S, et al. Impact of hepatic and extrahepatic insults on the outcome of acute-on-chronic liver failure. *J Clin Exp Hepatol*. 2017;7:9-15.
41. Bihari C, Patil A, Shasthry SM, Baweja S, Kumar G, Sarin SK. Viscoelastic test-based bleeding risk score reliably predicts coagulopathic bleeding in decompensated cirrhosis and ACLF patients. *Hepatol Int*. 2020;14:597-608.
42. Maipang K, Potranun P, Chainuvati S, et al. Validation of the prognostic models in acute-on-chronic liver failure precipitated by hepatic and extrahepatic insults. *PLoS One*. 2019;14:e0219516.
43. Nakayama N, Uemura H, Uchida Y, et al. Nationwide survey for patients with acute-on-chronic liver failure occurring between 2017 and 2019 and diagnosed according to proposed Japanese criteria. *J Gastroenterol*. 2021;56:1092-1106.
44. Bajaj JS, O'Leary JG, Reddy KR, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. *Hepatology*. 2012;56:2328-2335.
45. Rosenblatt R, Shen N, Tafesh Z, et al. The North American Consortium for the Study of End-Stage Liver Disease-Acute-on-Chronic Liver Failure Score accurately predicts survival: an external validation using a National Cohort. *Liver Transpl*. 2020;26:187-195.
46. 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;70:639-647.
47. Li F, Thuluvath PJ. EASL-CLIF criteria outperform NACSELD criteria for diagnosis and prognostication in ACLF. *J Hepatol*. 2021;75:1096-1103.

48. Vincent JL, Moreno R, Willatts S, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707-710.
49. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646-649.
50. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33:464-470.
51. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med*. 2008;359:1018-1026.
52. Ortiz M, Cordoba J, Doval E, et al. Development of a clinical hepatic encephalopathy staging scale. *Aliment Pharmacol Ther*. 2007;26:859-867.
53. Rahimi RS, Safadi R, Thabut D, et al. Efficacy and safety of ornithine phenylacetate for treating overt hepatic encephalopathy in a randomized trial. *Clin Gastroenterol Hepatol*. 2021;19:2626-2635.e7.
54. Bajaj JS, Frederick RT, Bass NM, et al. Overt hepatic encephalopathy: development of a novel clinician reported outcome tool and electronic caregiver diary. *Metab Brain Dis*. 2016;31:1081-1093.
55. Wehler M, Kokoska J, Reulbach U, Hahn EG, Strauss R. Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems. *Hepatology*. 2001;34:255-261.
56. Das V, Boelle P, Galbois A, et al. Cirrhotic patients in the medical intensive care unit: early prognosis and long-term survival. *Crit Care Med*. 2010;38:2108-2116.
57. Levesque E, Hoti E, Azoulay D, et al. Prospective evaluation of the prognostic scores for cirrhotic patients admitted to an intensive care unit. *J Hepatol*. 2012;56:95-102.
58. Farias AQ, Vilalta AC, Zitelli PM, et al. Genetic ancestry, race, and severity of acutely decompensated cirrhosis in Latin America. *Gastroenterology*. 2023. doi: 10.1053/j.gastro.2023.05.033
59. Mahmud N, Kaplan DE, Taddei TH, Goldberg DS. Incidence and mortality of acute-on-chronic liver failure using two definitions in patients with compensated cirrhosis. *Hepatology*. 2019;69:2150-2163.
60. Trebicka J, Fernandez J, Papp M, et al. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. *J Hepatol*. 2020;73:842-854.
61. Gustot T, Fernandez J, Garcia E, et al. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. *Hepatology*. 2015;62:243-252.
62. Engelmann C, Thomsen KL, Zakeri N, et al. Validation of CLIF-C ACLF score to define a threshold for futility of intensive care support for patients with acute-on-chronic liver failure. *Crit Care*. 2018;22:254.
63. 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;61:1038-1047.
64. Rosi S, Piano S, Frigo AC, et al. New ICA criteria for the diagnosis of acute kidney injury in cirrhotic patients: can we use an imputed value of serum creatinine? *Liver Int*. 2015;35:2108-2114.
65. European Association for the Study of the Liver Electronic address: easloffice@easloffice eu, European Association for the Study of the LivA – eng. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69:406-460.
66. 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;71:148-155.
67. Sargenti K, Prytz H, Nilsson E, Kalaitzakis E. Predictors of mortality among patients with compensated and decompensated liver cirrhosis: the role of bacterial infections and infection-related acute-on-chronic liver failure. *Scand J Gastroenterol*. 2015;50:875-883.
68. Jalan R, Pavesi M, Saliba F, et al. The CLIF Consortium Acute Decompensation score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. *J Hepatol*. 2015;62:831-840.
69. Cao Z, Liu Y, Zhu C, et al. Bacterial infection triggers and complicates acute-on-chronic liver failure in patients with hepatitis B virus-decompensated cirrhosis: a retrospective cohort study. *World J Gastroenterol*. 2020;26:645-656.
70. Mahmud N, Reddy KR, Taddei TH, Kaplan DE. Type of infection is associated with prognosis in acute-on-chronic liver failure: a National Veterans Health Administration Study. *Dig Dis Sci*. 2023;68:1632-1640.
71. Bajaj JS, Reddy RK, Tandon P, et al. Prediction of fungal infection development and their impact on survival using the NACSELD cohort. *Am J Gastroenterol*. 2018;113:556-563.
72. Fernandez J, Acevedo J, Wiest R, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. *Gut*. 2018;67:1870-1880.
73. Sundaram V, Jalan R, Shah P, et al. Acute on chronic liver failure from nonalcoholic fatty liver disease: a growing and aging cohort with rising mortality. *Hepatology*. 2021;73:1932-1944.
74. Sundaram V, Kogachi S, Wong RJ, et al. Effect of the clinical course of acute-on-chronic liver failure prior to liver transplantation on post-transplant survival. *J Hepatol*. 2020;72:481-488.
75. Antunes AG, Teixeira C, Vaz AM, et al. Comparison of the prognostic value of Chronic Liver Failure Consortium scores and traditional models for predicting mortality in patients with cirrhosis. *Gastroenterol Hepatol*. 2017;40:276-285.
76. Piano S, Tonon M, Vettore E, et al. Incidence, predictors and outcomes of acute-on-chronic liver failure in outpatients with cirrhosis. *J Hepatol*. 2017;67:1177-1184.
77. Zaccherini G, Baldassarre M, Bartoletti M, et al. Prediction of nosocomial acute-on-chronic liver failure in patients with cirrhosis admitted to hospital with acute decompensation. *JHEP Rep*. 2019;1:270-277.
78. 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.
79. Sarin SK, Choudhury A. Acute-on-chronic liver failure: terminology, mechanisms and management. *Nat Rev Gastroenterol Hepatol*. 2016;13:131-149.

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