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Intensive Care Management of Post-Transplant Patients

A Guide for Critical Care Specialists

(Liver, Kidney, Pancreas and Small Bowel Transplant)

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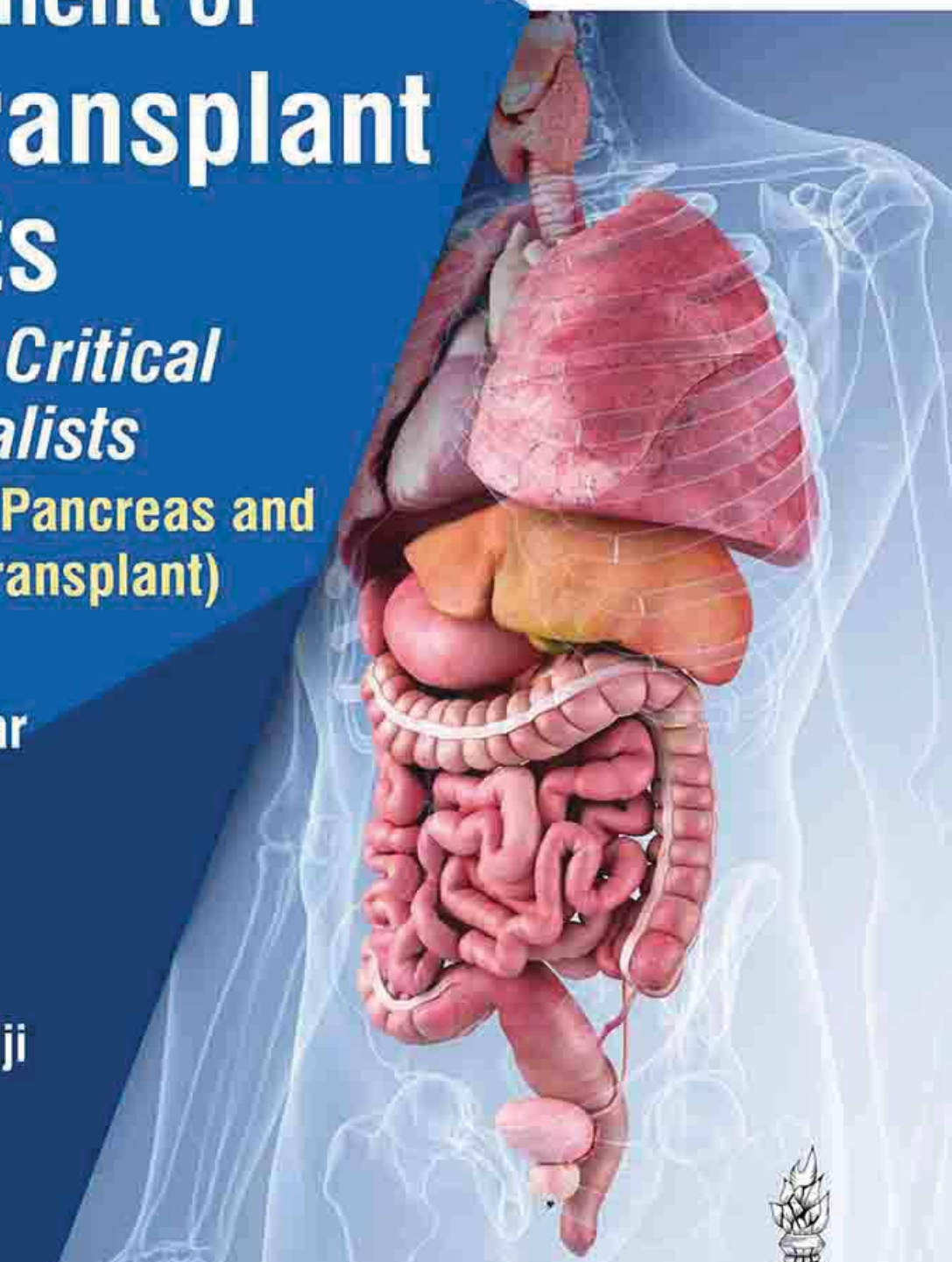

Volume 3

JAYPEE

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CHAPTER 1

Indications of Liver Transplantation in the Setting of Acute Liver Failure, Acute-on-Chronic Liver Failure, and Chronic Liver Disease

Aditya Kunte, Johann Paulo Guzman, Akash Shukla, Ravi Mohanka

INTRODUCTION

Liver disease is a significant global health challenge, accounting for nearly 2 million (4% of all) deaths, two third of them occurring in men.[1] It also contributes to high disability-adjusted life years (DALYs), especially in the young population, and poses an economic burden of more than 30 billion USD in the US alone. There has been a consistent increase in the incidence of liver disease and liver-related deaths over the past decade, thus necessitating a coordinated response to improve prevention, early detection, and treatment strategies.[1,2]

Dr Thomas Starzl performed the first successful liver transplantation (LT) from a deceased (cadaveric) donor liver transplantation (DDLT) in 1968.[3] Initial challenges with high rates of surgical complications, rejection, and graft loss have improved with advances in surgical techniques, safety of anesthesia, specialty critical care, diagnostic and immunological tests, organ allocation systems, better organ preservation methods, immunosuppressive, antimicrobial and other medicines, leading to excellent short- and long-term outcomes. Currently, LT is the standard of care for end-stage liver disease (ESLD) treatment, with 34,694 liver transplants performed globally in 2023, an increase of 6.5% from 2020 and 20% from 2015.[4] Although there is high variability between countries, LT continues to increase globally **(Figs. 1 and 2)**.

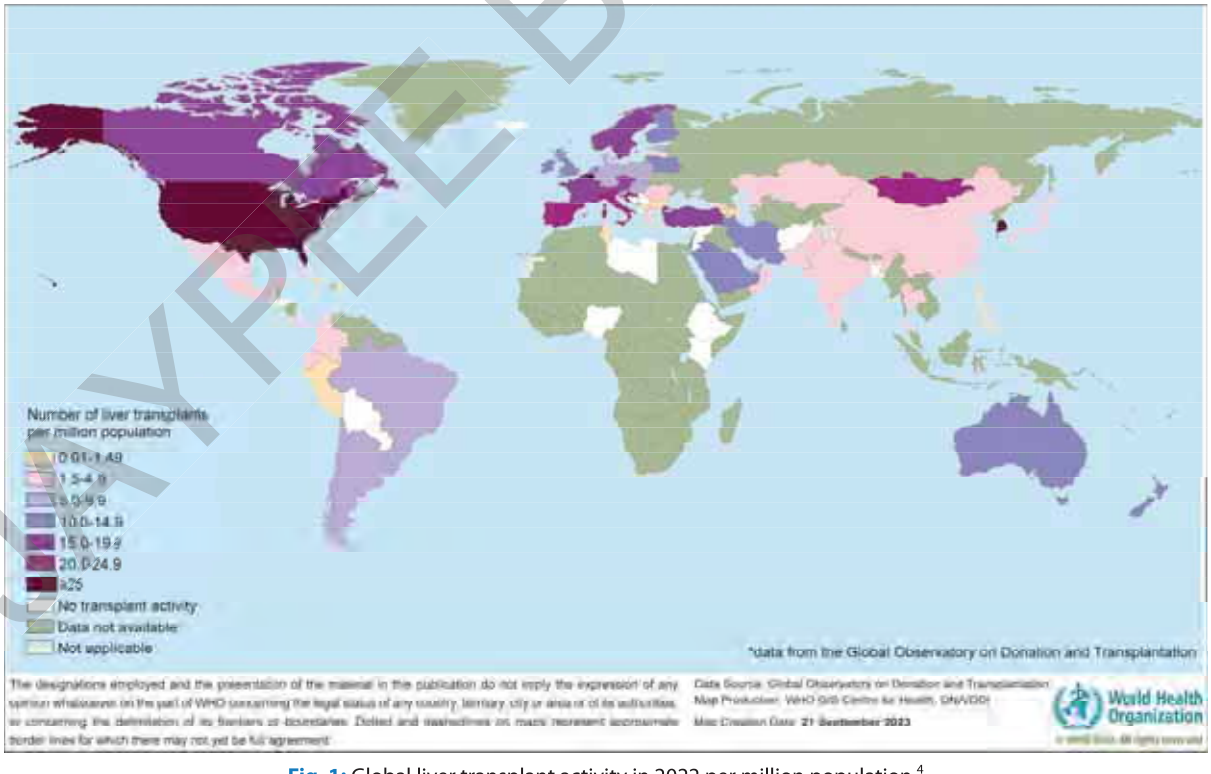

Fig. 1: Global liver transplant activity in 2022 per million population.[4]

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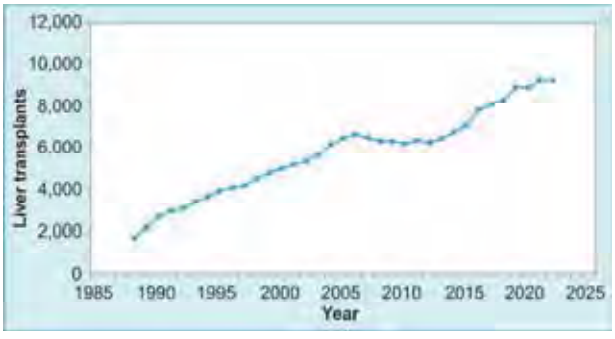

Fig. 2: Globally increasing number of transplants.
Source: OPTN/SRTR Annual Data Reports: Liver. Scientific Registry of Transplant Recipients. U.S. Department of Health and Human Resources (Kwong).[5]

The demand for LT far exceeds available organs, leading to a huge and widening gap. This has been partially addressed by expanding the donor pool using livers from extended criteria donors (ECD), donation after circulatory death (DCD), and living donor liver transplant (LDLT). Almost 90% of LTs in Western countries are DDLT, whereas the majority in Asian countries are LDLT,[4] which may be because of deceased donor organ availability, cultural and religious beliefs, and availability of surgical expertise and infrastructure for organ allocation and transport **(Fig. 3)**.

Liver Disease: Spectrum of Clinical Presentation and Indications for Liver Transplantation

The most common presentation of liver disease is chronic liver failure, which progresses through stages of steatosis, inflammation, fibrosis, and cirrhosis. Long-term chronic sustained injury often leads to repair by fibrosis and compartmentalization of hepatocytes into nodules, making regeneration ineffective and the damage irreversible. Most patients with cirrhosis have adequate reserve/functional capacity and remain compensated and asymptomatic. However, the natural history of liver cirrhosis is often progressive, marked by decompensations and/or HCC. Effective treatment of the underlying etiology can halt the progression of CLD and potentially reduce the need for LT.

Liver disease in patients with a healthy background liver, without underlying CLD, may present with rapid-onset persistent jaundice, coagulopathy without encephalopathy, i.e., severe acute liver injury (sALI), or with encephalopathy, i.e., ALF, or with the protracted course and ascites, i.e., subacute hepatic failure (SHF) **(Table 1)**. Even if the injury/damage/inflammation/necrosis is widespread/extensive, spontaneous recovery with regeneration is common if there is adequate hepatocyte mass. If the magnitude of injury is overwhelming and hepatocyte mass is inadequate for regeneration, and/or there is failure of regeneration, it may lead to rapid deterioration, severe systemic inflammatory response syndrome (SIRS), multiorgan dysfunction syndrome (MODS), or cerebral edema, which could be fatal within days to weeks. Historically, ALF patients had >80% risk of mortality, whereas an emergency LT is often life-saving. When a stable CLD patient deteriorates rapidly due to acute events such as infection, variceal bleeding, acute HBV flare, or others, it is called ACLF **(Table 1; Fig. 4)**.[6]

Liver transplantation should be offered to patients at an optimum time in the course of their liver disease and performed at the most appropriate time when the expected risk of mortality due to the natural progression of liver disease is higher than the risk of LT. If done too early, the patient may be deprived of a chance at spontaneous recovery, and if delayed beyond a point, they may be too sick and have lower chances of success of LT.[7] LT should be done when:

- The recipient has irreversible acute or CLD that is expected to be fatal without LT.
- The patient has sufficient reserve to survive the operation and recover in the perioperative period.
- The candidate is expected to have significant survival and quality-of-life (QoL) benefits from LT.

Over the past few decades, LT indications have evolved due to changes in the epidemiology of liver diseases, the introduction of effective antiviral drugs, universal vaccination, and lifestyle changes, especially during the COVID-19 pandemic. Alcohol-associated liver disease (ALD) and metabolic syndrome-associated steatotic liver disease (MASLD) are now leading indications for LT, whereas hepatitis C (HCV) and hepatitis B (HBV) viral hepatitis are declining.[2] In addition to chronic liver disease (CLD), LT is performed for acute liver failure (ALF), acute-on-chronic liver failure (ACLF), liver tumors, and inborn errors of metabolism (IEM). The success of LT as a curative therapy for hepatocellular cancer (HCC) has prompted the growth of transplant oncology as an emerging specialty.

LIVER TRANSPLANTATION FOR CHRONIC LIVER DISEASE

Chronic liver disease is the most common indication for LT. Cirrhosis has increased by 74.5% from 1990 to

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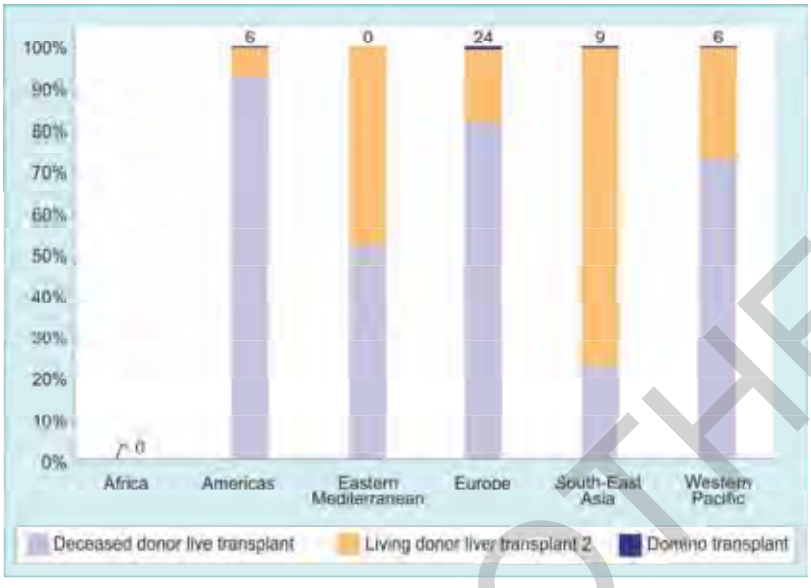

	African region	*Region of the Americas*	*Eastern Mediterranean region*	*European region*	*South-East Asian region*	*Western Pacific region*
Number of liver transplants: Absolute per million population (PMP)	0 (0.0)	13,387 (13.6)	1,817 (3.9)	9,840 (14.3)	4,067 (2.5)	8,325 (4.7)
% DDLT	0	88	59	82	19	71
Countries with liver TX activity/ (total countries in the region)	0 (46)	15 (35)	7 (22)	36 (53)	2 (11)	8 (27)
Liver TX centers (millions of inhabitants/center)	0	404 (2.4)	35 (13.2)	229 (3.0)	247 (6.7)	231 (7.7)

Fig. 3: Variations in liver transplant practices in different WHO regions globally.[4]
(PMP: per million population; WHO: World Health Organization)

TABLE 1: Phenotypic spectrum of liver failure.

Liver failure syndrome	*Definition/description*	*Outcome*
Severe acute liver injury (sALI)	Jaundice and prolonged PT/INR >1.5 over days/weeks	Usually recovers spontaneously, some may progress to ALF
Acute liver failure (ALF)	• Encephalopathy associated with jaundice and PT/INR >1.5 occurring over hours/days (up to 26 weeks) • In children, sALI with PT-INR >2 is classified as ALF, even without encephalopathy	Associated with a high 15-day mortality
Subacute hepatic/liver failure (SHF)	*A variant of ALF:* Persistent jaundice and progressive followed by ascites beyond 4 and within 24 weeks	High mortality over 6 months
Chronic liver disease (decompensated cirrhosis)	Cirrhosis and portal hypertension, characterized by progressive ascites, jaundice, encephalopathy, and coagulopathy	Mortality is often proportional to disease severity
Acute-on-chronic liver failure (ACLF)	Acute deterioration of chronic liver disease leading to multiorgan failure	High mortality in 4 and 12 weeks

(INR: international normalized ratio; PT: prothrombin time)

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2017 **(Fig. 4)**. East Asia, South Asia, and Southeast Asia have the highest number of cases. At the same time, the Caribbean and Latin American regions, most particularly the United Arab Emirates, have shown the greatest increase. Major drivers of LT for CLD are chronic HBV, chronic HCV, ALD, MASLD in adults, and biliary atresia in children. These exhibit significant geographic variations. The prevalence of HBV, HCV, ALD, and MASLD-related liver cirrhosis increased by 29.2%, 28.7%, 80%, and 125.6%, respectively **(Fig. 5)**.

Global Geographical Trends in CLD

The burden of HBV is highest in the Western Pacific, followed by Africa, Eastern Mediterranean, Southeast Asia, Europe, the Americas,[3] and Qatar, which corresponds to lower vaccination rates in these regions. With a global drive for universal vaccination, there has been a 31.3% decrease in the prevalence of HBV between 1990 and 2019, most significantly in children younger than 5 years (76.8%).[8-10] The use of nucleoside analogs for long-term suppression of the virus has also altered the natural history of HBV; although a functional cure is rare, the risk of HCC is reduced, but not eliminated.[11] HCV is the highest in Eastern Europe and Central Asia, with most cases in South Asia, East Asia, and the UAE.[12] In the US, the incidence of HCV infections among donors has increased between 2010 and 2021,[13] probably due to an increase in young, often suburban heroin injection drug users; infections in non-hospital healthcare (clinic) settings; and sexual transmission among HIV-infected persons.[14] Alcohol consumption caused almost half of all cases and deaths attributed to CLD in 2016. While the burden of ALD impacts most regions of the world, in 2019, Mongolia, Kazakhstan, El Salvador, Guatemala, Greenland, Kyrgyzstan, Poland, Rwanda, Ireland, and Brazil were most affected by ALD.[8,9] MASLD is the most common cause of CLD in many regions of the world,[2] with a 15.78% prevalence in North America, an estimated 42.4%, and a projected prevalence of >55% by 2040.[15] There is a shift in the disease burden to Middle Eastern and North African, Asian, and Latin American countries, with 26.5% prevalence in the Middle East. In Asia, the increase in MASLD is driven by China, India, and Indonesia.[16]

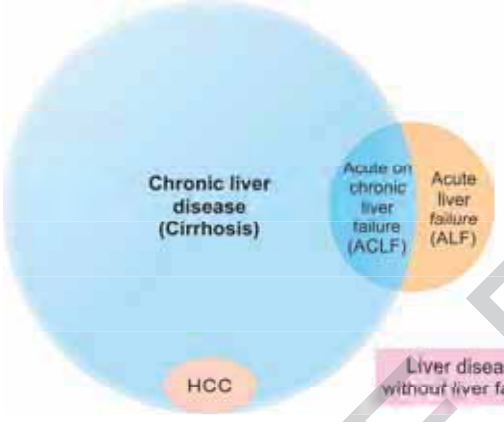

Fig. 4: Clinical presentations of liver diseases requiring a liver transplant.

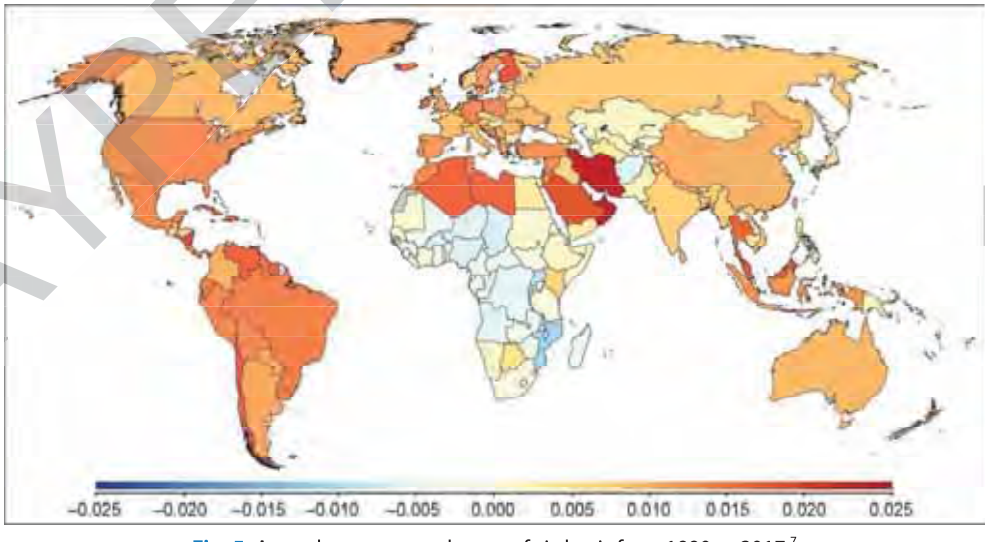

Fig. 5: Annual percentage change of cirrhosis from 1990 to 2017.[7]

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Globally, nonalcoholic fatty liver disease (NAFLD) has increased at an annual rate of 1.47%/year from 10.5% in 1990 to 16.0% in 2019[17] **(Figs. 6 to 8)**.

With the increasing burden of cirrhosis worldwide, the need for LT and its activity has increased and its etiologies have changed **(Fig. 9)**.

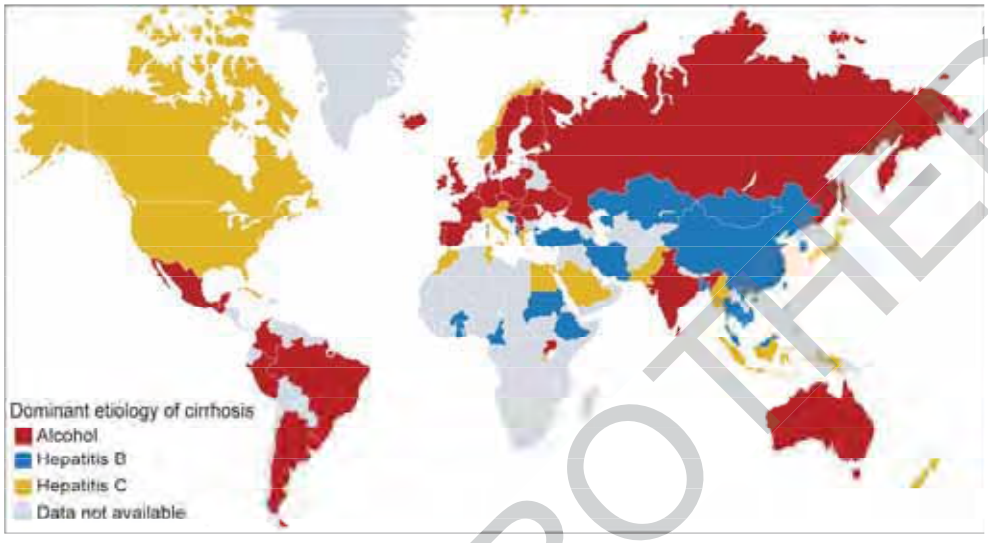

Fig. 6: Geographic variations in the dominant etiology of cirrhosis.[18]

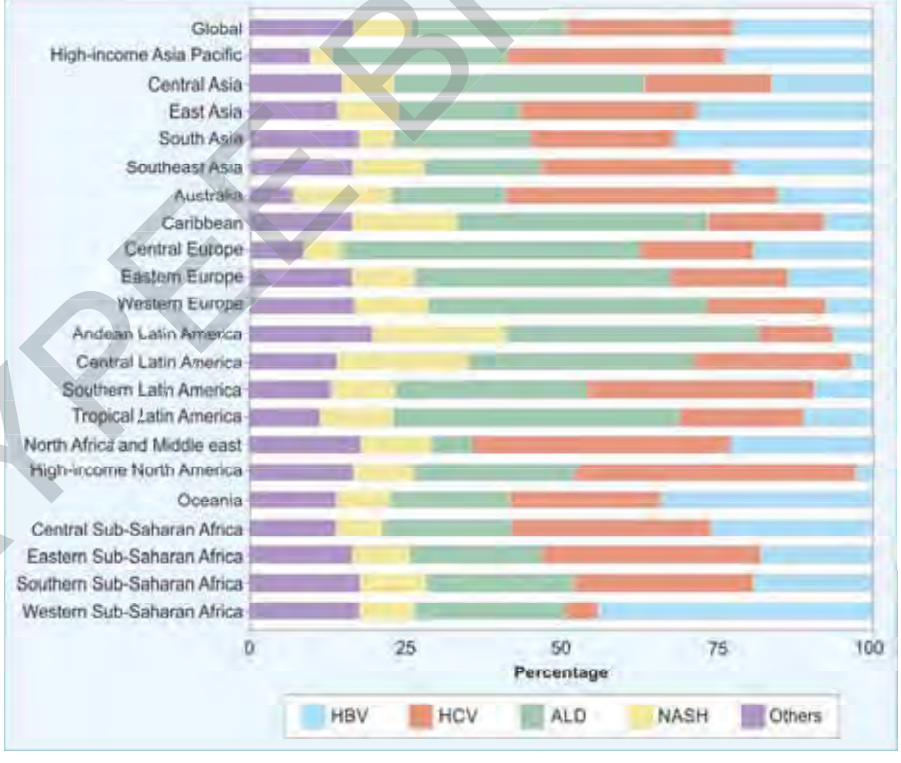

Fig. 7: Variations in dominant etiology of cirrhosis in various WHO regions.[19] (ALD: alcoholic liver disease; HBV: hepatitis B virus; HCV: hepatitis C virus; NASH: non-alcoholic steatohepatitis; WHO: World Health Organization)

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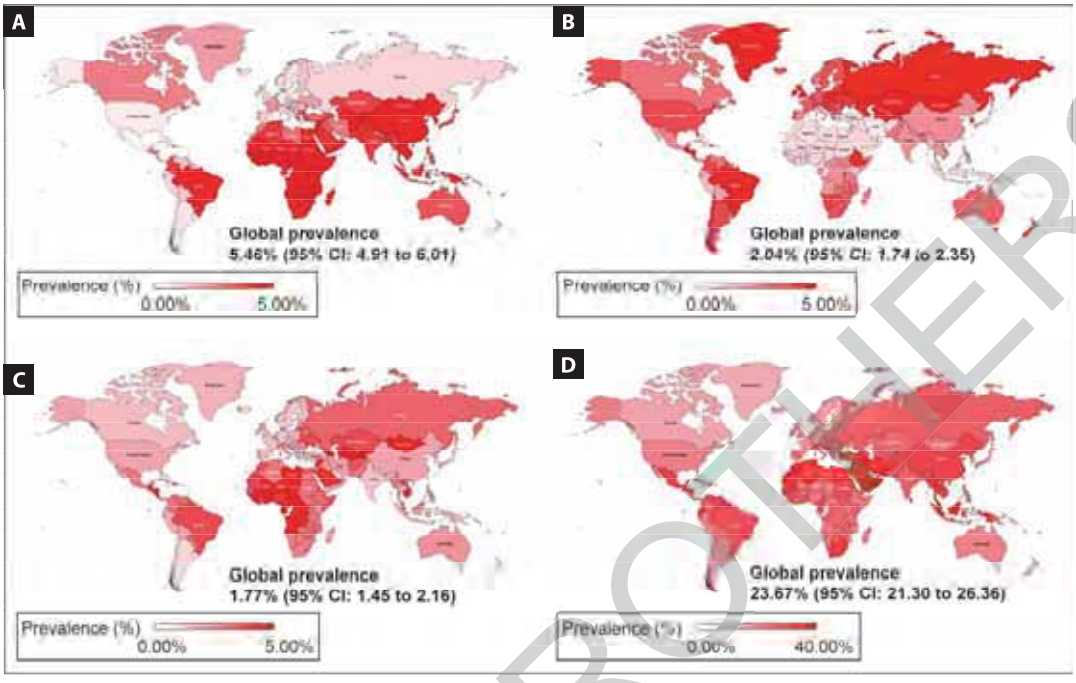

Figs. 8A to D: (A) Prevalence of HBV; (B) Prevalence of HCV; (C) Prevalence of ALD; (D) Prevalence of MAFLD (in adults aged ≥20 years).[4] (ALD: alcoholic liver disease; CI: confidence interval; HBV: hepatitis B virus; HCV: hepatitis C virus; MAFLD: metabolic associated fatty liver disease)

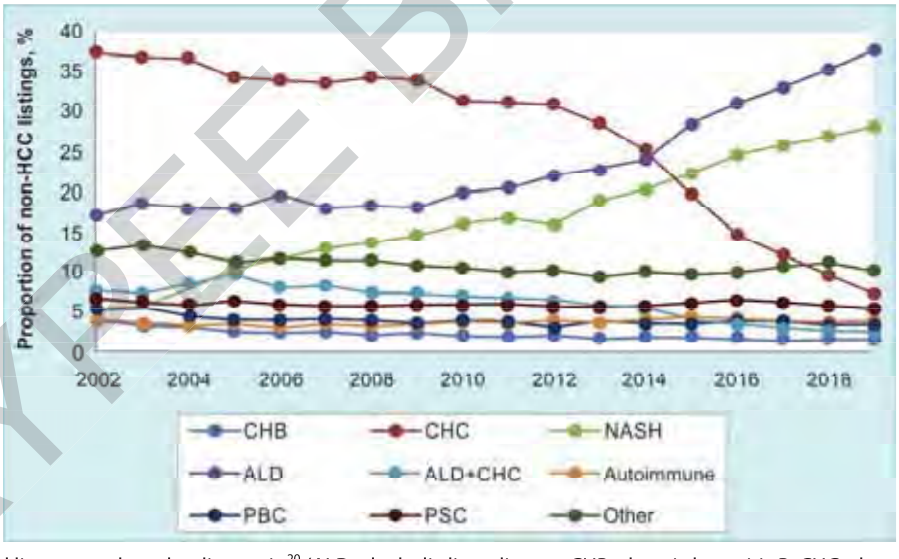

Fig. 9: US total liver transplants by diagnosis.[20] (ALD: alcoholic liver disease; CHB: chronic hepatitis B; CHC: chronic hepatitis C; HCC: hepatocellular carcinoma; NASH: non-alcoholic steatohepatitis; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis)

Assessment of Severity of CLD and Indication for LT

Liver transplantation in CLD is generally considered when patients transition from compensated to decompensated cirrhosis (about 5–7% per year), as this seminal event in the natural history of cirrhosis reduces their median survival from >12 years to ~2 years.[21] **(Table 2)**. Children with liver disease may also experience growth failure and benefit from LT before puberty to enable catch-up growth.

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TABLE 2: Complications/decompensations of CLD and their prognosis.

Complications/Decompensation	*Incidence*	*Expected median survival*	*Mortality risk*
Hepatic encephalopathy		6–9 months	
Variceal bleed		• CTP-A: 5 years • CTP-B: 3 years • CTP-C: 3 months	
Ascites	5–10%/year	20 months	
Refractory ascites	10–15% from ascites	6 months	50% at 6–12 months
Spontaneous bacterial peritonitis (SBP)	• Outpatient: 1.5–3.5% • In-patient: 10%	9 months	In each episode 20%
HRS-1 (HRS-AKI)		2 weeks	
HRS-2 (HRS-CKD)		6 months	
Hepatic hydrothorax			
Hepatopulmonary syndrome	10–17%	Severe: 10.5 months	
Portopulmonary hypertension		2.8 years	
Malnutrition, sarcopenia, and frailty		8.5 months	

(CLD: chronic liver disease; CTP: Child-Turcotte-Pugh; HRS-AKI: hepatorenal syndrome–acute kidney injury; HRS-CKD: hepatorenal syndrome–chronic kidney disease)

Decompensation is more commonly, objectively, and comprehensively classified using the Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores for comparison between patients **(Tables 3 and 4)**.[22]

The CTP score is subjective and has limited discriminatory power; therefore, it was replaced by the MELD score for organ allocation in 2002 in the USA, which is more objective and reliable for predicting mortality. Subsequent modifications of the MELD score have addressed some of its deficiencies; the MELD-Na incorporates hyponatremia as a surrogate marker for the degree of ascites, and the more recent MELD 3.0 accounts for interactions between bilirubin, sodium, and albumin and has a better predictive value.[23] Several countries have adopted the MELD score or its modifications for organ allocation in their systems.

Liver transplantation improves survival and quality of life for CTP >7.[21] DDLT confers a survival advantage compared to continuing medical management at a MELD cutoff of >14, and with an LDLT, the benefit may accrue at a score >10.[24] LT candidates with stage 3 acute kidney injury (AKI), needing dialysis, with estimated glomerular filtration rate (eGFR) <35 by MDRD-6 (modification of diet in renal disease-6) for >4 weeks or with evidence of structural renal disease should be considered for simultaneous liver-kidney transplant (SLKT).[25]

TABLE 3: Child-Turcotte-Pugh (CTP) score.

	Points		
Parameters	*1*	*2*	*3*
Encephalopathy	None	Grade 1–2	Grade 3–4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Total bilirubin (mg/dL)	<2	2–3	>3
PT (sec prolonged) or INR	<4	4–6	>6
	<1.7	1.7–2.3	>2.3

CTP classification is based on the sum of all the above components
Class A = 5–6 points, *Class B* = 7–9 points, *Class C* = 10–15 points

CTP classification and prognosis

Class	*Score*	*Expected 1-year survival*	*Expected 5-year survival*
A	5–6	90%	90%
B	7–9	80%	70%
C	10–15	45%	38%

(INR: international normalized ratio; PT: prothrombin time)

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TABLE 4: Model for End-Stage Liver Disease (MELD) score, its variations, and prognosis.

MELD	*MELD Na*	*UK MELD*	*MELD 3.0*
$9.57 \times \text{Log}_e$ (creatinine) + $3.78 \times \text{Log}_e$ (bilirubin) + $11.20 \times \text{Log}_e$ (INR) + 6.43	MELD + $1.32 \times (137 - \text{Na}) - 0.033 \times \text{MELD} \times (137 - \text{Na})$	$1.485 \times \text{Log}_e$ (creatinine) + $3.13 \times \text{Log}_e$ (bilirubin) + $5.395 \times \text{Log}_e$ (INR) + $81.565 \times \text{Log}_e$ (Sodium) + 435	1.33 (if female) + $4.56 \times \text{Log}_e$ (bilirubin) + $0.82 \times (137 - \text{Na}) - 0.24 \times (137 - \text{Na}) \times \text{Log}_e$ (bilirubin) + $9.09 \times \text{Log}_e$ (INR) + $11.14 \times \text{Log}_e$ (creatinine) + $1.85 \times (3.5 - \text{albumin}) - 1.83 \times (3.5 - \text{albumin}) \times \text{Log}_e$ (creatinine) + 6
125 < Na <137 mmol/L, and MELD Na is applied when MELD >11. A value of 4.0 is assigned if serum creatinine ≥4.0 or if the patient received ≥2 dialysis sessions within the prior week. The maximum serum creatinine has been lowered from 4.0 to 3.0 in the MELD 3.0			

Survival MELD score	*3 months*	*1 year*
0–9	98%	90%
10–19	94%	80%
20–29	81%	66%
30–39	48%	33%
>40	29%	<5%

(INR: international normalized ratio)

In addition to these common etiologies, CLD maybe caused by autoimmune, cholestatic, metabolic, vascular, and other etiologies. In about 20% of cases, the etiology may not be identified, i.e., cryptogenic. In some diseases, these scores do not accurately reflect the severity of their liver disease, and alternative scoring systems are used and indications for LT may be different **(Table 5)**.

LIVER TRANSPLANTATION FOR ACUTE LIVER FAILURE

Common Etiologies of ALF

- *Hepatitis A:* <1% of acute hepatitis A virus (HAV) infections result in ALF. HAV generally causes subclinical hepatitis in children and more severe infection in adults.
- *Hepatitis B:* This is an uncommon cause of ALF, caused by acute infection or reactivation in chronic HBV, both of which can be differentiated by IgM anti-HBc titers and HBV viral load and have markedly different prognoses.
- *Hepatitis E:* This is the most common cause of acute sporadic and epidemic hepatitis and accounts for 10–40% of acute hepatitis and 15–45% of ALF in India, with high mortality.
- *Toxins/drug-induced liver injury (DILI):* Paracetamol toxicity constitutes nearly half of all ALF in the West, others being antibacterials, anti-tuberculosis (TB) drugs, herbal and dietary supplements, antiepileptics, nonsteroidal anti-inflammatory drugs (NSAIDs), mushrooms (Amanita), and others. In India, paracetamol only constitutes ~1% of all drug-induced ALF, the more common ones being anti-TB drugs, complementary and alternative medicines (CAM), antiepileptic drugs (first generation), sulfonamides, antiretroviral drugs, yellow phosphorus (rat poison), and others **(Box 1)**.
- *Pregnancy:* Pregnant women are more likely to have ALF than other women and men. It is more common in the third trimester and is most commonly caused by viral hepatitis, hepatitis E virus (HEV) (60%), HBV, HAV, and rarely herpes simplex virus (HSV) and varicella-zoster virus (VZV). Acute fatty liver of pregnancy (AFLP) and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndromes are specific for pregnancy and may improve with termination.
- *Vascular causes:* ALF may be seen in shock liver after cardiac arrest, significant hypovolemia/hypotension, or severe congestive heart failure. About 1% of cases of Budd–Chiari syndrome present with ALF.

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TABLE 5: Scoring systems and indications for liver transplantation in selected chronic liver diseases.[25-29]

Disease	*Scoring system*	*Indication for LT*
Primary sclerosing cholangitis (PSC)	*Mayo PSC risk score:* 0.03 × (*age* in years) + 0.54 × log (*bilirubin* in mg/dL) + 0.54 × log (*AST* in IU/L) + 1.24 × (history of *variceal bleeding*) – 0.84 × (*albumin* in g/dL)	• Decompensated CLD • Recurrent cholangitis (≥2 episodes in 1 year requiring hospitalization) • Intractable pruritus with an unacceptable quality of life
Primary biliary cirrhosis (PBC)	*Mayo PBC risk score:* 0.871 × $\log_e$ (*bilirubin* in mg/dL) – 2.53 × $\log_e$ (*albumin* in g/dL) + 0.039 × (*age* in years) + $\log_e$ × (*prothrombin time* in seconds) + 0:859 (if *edema* is present)	• MRS ≥7.8 • Decompensated cirrhosis • Intractable pruritus • Profound disabling fatigue • Severe osteoporosis
	• UK-PBC score • *Baseline values:* Albumin, platelet count • *Values after 12 months of UDCA therapy:* Bilirubin, transaminases, alkaline phosphatase	Continuous score estimating 5-, 10-, and 15-year risk of death or liver transplant
	GLOBE score: Bilirubin, alkaline phosphatase, albumin, platelet count at 12 months, age at baseline	A score >0.3 is associated with significantly lower transplant-free survival
Alcoholic hepatitis	*Maddrey discriminant function (DF):* 4.6 × (prolongation of *prothrombin time* in seconds) + serum *bilirubin* (mg/dL)	DF >32 with hepatic encephalopathy >50% mortality within 28 days
	Glasgow Alcoholic Hepatitis Score (GAHS): Based on age, serum bilirubin, blood urea nitrogen, prothrombin time, and the peripheral leukocyte count	GAHS ≥9 predicts 28- and 84-day mortality
	Lille model: Age, renal insufficiency, albumin, prothrombin time, bilirubin, and the evolution of bilirubin on day 7 in response to steroids	Predicts 6-month mortality

(AST: aspartate aminotransferase; CLD: chronic liver disease; LT: liver transplantation; MRS: Mayo risk score; UDCA: ursodeoxycholic acid)

BOX 1: Drugs causing idiosyncratic reactions leading to acute liver failure.

Single agents causing heapatotoxicity

Isoniazid: • Valproic acid • Carbamazepine • Efavirenz • Methyldopa • Dapsone • Labetalol • Disulfiram • Gemtuzumab • Propylthiouracil • Phenytoin	*Pyrazinamide:* • Diclofenac • Abacavir • Ketoconazole • Etodolac • Tolcapone • MDMA (Ecstasy) • Terbinafine • Ciprofloxacin • Nicotinic acid • Sulfasalazine	*Isoflurane:* • Itraconazole • Doxycycline • Didanosine • Allopurinol • Amiodarone • Cocaine • Nitrofurantoin • Imipramine • Statins

Combination agents with enhanced toxicity

• Trimethoprim-sulfamethoxazole	• Rifampin–Isoniazid	• Amoxicillin–clavulanate

Herbal products/dietary supplements associated with hepatotoxicity

• Kava • Herbalife • Comfrey	• Greater celandine • LipoKinetix • Senecio	• He Shon Wu • Hydroxycut • Ma Huang

(MDMA: 3,4-methylenedioxymethamphetamine)

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- *Autoimmune hepatitis* (AIH) may account for 8–30% of all ALFs. It should be suspected in patients with autoantibodies, high globulins, and other autoimmune diseases. A liver biopsy is required for diagnosis. Patients with high-grade hepatic encephalopathy, high MELD scores, and/or lack of improvement within 7 days of steroids should be considered for LT.
- *Rare diseases* such as Reye's syndrome, hemophagocytic lymphohistiocytosis (HLH), and extensive malignant infiltration of the liver may also present with ALF.
- *Indeterminate/seronegative (non-A–E) hepatitis*: All etiological workup may be negative in about 15–47% of adult and 13–20% of children with ALF. They are generally tested for hepatitis A–E, although rare viruses [dengue, HSV, Epstein–Barr virus (EBV), VZV, and others] may be responsible.

Prognostication and Classification in Acute Liver Failure

Several factors, such as age, severity of insult, organ failure, and comorbidities, have been identified to predict spontaneous recovery in ALF, although etiology and rapidity of progression [measured by jaundice–encephalopathy interval (JEI)] are most significant. JEI is most often used for the subclassification of ALF **(Table 6)**. Counterintuitively, the highest rate of spontaneous recovery is seen in patients with rapidly progressive (shorter JEI) ALF, whereas a slower clinical course (longer JEI), with modest coagulopathy and lower incidence of cerebral edema, exhibits much lower rates of spontaneous recovery and is most likely to require LT **(Fig. 10)**.

Several scores have been described to prognosticate disease progression in ALF; King's College criteria is the most widely used tool, although several etiology-specific and dynamic scoring systems have also been described **(Table 7)**. They are aimed at differentiating patients into one of the following categories:

TABLE 6: Subclassifications of ALF based on jaundice–encephalopathy interval (JEI).

Classification system	*Jaundice–encephalopathy interval*
Trey and Davidson[25]	≤8 weeks
Fulminant hepatitis[26] • Acute • Subacute	≤8 weeks ≤10 days 11–56 days
• Fulminant hepatic failure[27] • Subfulminant hepatic failure	≤2 weeks 2 weeks–to 3 months
British classification[28] • Hyperacute liver failure • Acute liver failure • Subacute liver failure • Late-onset	 ≤7 days 8–28 days 29–72 days 56–182 days
International Association for Study of the Liver (IASL)[29] • Hyperacute • Fulminant • Subacute	 ≤10 days 10–30 days 5–24 weeks (with ascites and/or HE)
AASLD[30]	≤26 weeks
Intractable Hepato-Biliary Diseases Study Group of Japan[31] • ALF without hepatic coma • ALF with hepatic coma – Acute – Subacute	 ≤8 weeks ≤10 days 11–56 days

(AASLD: American Association for the Study of Liver Diseases; ALF: acute liver failure; HE: hepatic encephalopathy)

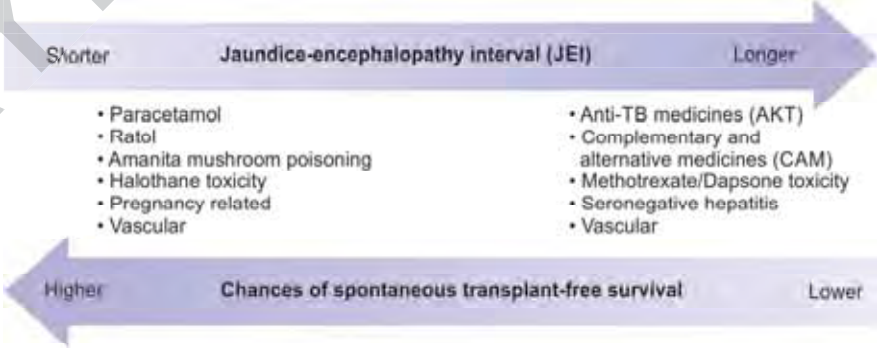

Fig. 10: Inverse relationship of spontaneous recovery to encephalopathy interval.

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TABLE 7: Prognostic scores in acute liver failure.

Criteria, year, etiologies	*Prognostic parameters*	*Criteria performance*
King's College Criteria for paracetamol toxicity[31]	Arterial pH <7.3 (independent of HE grades) OR Grade 3 or 4 encephalopathy and PT >100 seconds and Serum creatinine >3.4 mg/dL	Sensitivity 69%, specificity 92%
King's College Criteria for nonparacetamol etiologies[31]	PT >100 seconds (independent of HE grades) OR Any three of the following variables (independent of HE grades): 1. *Age:* <10 or >40 years 2. *Etiology:* Non-A, non-B, halothane hepatitis, idiopathic drug reactions 3. Duration of jaundice before onset of encephalopathy >7 days 4. PT >50 seconds 5. Serum bilirubin >18 mg/dL	
Bernuau et al.[32] HBV	Age, factor V levels	
Bismuth et al.[33] Mixed etiologies	Age, factor V levels, HE grades 3–4	
Hadem et al.[34] BiLE score Mixed etiologies	Etiology, bilirubin, lactate	
Dhiman et al.[35] Mixed etiologies	Any three of the six parameters: 1. Age >50 years 2. Prothrombin time >35 seconds 3. Creatinine >1.5 mg/dL 4. Jaundice to encephalopathy >7 days 5. HE grades 3–4 6. Cerebral edema	Superior to KCH and MELD
Kumar et al.[36] ALFED dynamic criteria Indian, HAV, HEV	• Age >50 years, time from JEI > 7 days • PT >35 seconds, serum creatinine >1.5 mg/dL	Late clinical complications associated with poor outcomes
Bechmann et al.[37] Mixed etiologies	Creatinine, INR, cytokeratin 18	Superior to KCH and MELD
Bernal et al.[38] Paracetamol	Serum lactate (early 3.5 mmol/L, postresuscitation 3.0 mmol/L)	
Schmidt and Dalhoff[39] Paracetamol	Serum phosphate (1.2 mmol/L, 48–96 hours after overdose)	Not superior to KCH
Schmidt and Larsen[40] Paracetamol	MELD score	• Sensitivity 60% • Not superior to KCH
Rutherford et al.[41] ALFSG index Mixed etiologies	INR, serum bilirubin, phosphate, M30, encephalopathy grade	• Sensitivity 86% • Superior to KCH and MELD
Taylor et al.[42] HAV	ALT <2,600 IU/L, creatinine >2.0 mg/dL Mechanical ventilation, inotropes	Superior to KCC and MELD
Ganzert et al.[43] Amanita phyllodes	Prothrombin index <25%, creatinine >106 µmol/L Applicable from day 3	Sensitivity 100%, specificity 98%

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Criteria, year, etiologies	*Prognostic parameters*	*Criteria performance*
Westbrook et al.[44] Pregnancy-related	Lactate >2.8 mg/dL, HE	*Lactate*: Sensitivity 73%, specificity 75% *Lactate + HE:* Sensitivity 90%, specificity 86% Predicting death and LT
Nonparacetamol	MELD >32	Sensitivity 76%, specificity 67% Not superior to KCC
Clichy criteria[45] (Paracetamol/HBV)	Factor VIII/V ratio >30, factor V <10%	Sensitivity 91%, specificity 91% Superior to KCC
Paracetamol	Arterial lactate 3.5 mmol/L on admission, 3 mmol/L postresuscitation	Sensitivity 81%, specificity 95% Superior to KCC
Paracetamol	Serum phosphate 1.2 mmol/L, 48–96 hours after overdose	Sensitivity 89%, specificity 100% Superior to KCC
Paracetamol	MELD >33 at onset of HE	Sensitivity 60%, specificity 69% Not superior to KCC
NHS criteria for paracetamol toxicity	• pH <7.25 >24 hours after overdose and after fluid resuscitation • Significant liver injury and coagulopathy following exclusion of other causes of hyperlactatemia (e.g., pancreatitis, intestinal ischemia) after adequate fluid resuscitation – Arterial lactate >5 mmol/L on admission – Arterial lactate >4 mmol/L after 24 hours of fluid resuscitation – Clinical hepatic encephalopathy • *All three criteria fulfilled:* – Prothrombin time >100 seconds or INR >6.5 – Serum creatinine >300 µmol/L (3.39 mg/dL) or anuria – Grade 3–4 encephalopathy • Two of the above three criteria from the category with clinical evidence of deterioration (e.g., increased ICP, FiO_2 >50%, increasing inotrope requirements) in the absence of clinical sepsis	
NHS criteria for favorable etiologies (HAV, HEV, Ecstasy, Cocaine toxicity, etc.)	• Clinical hepatic encephalopathy is mandatory • Prothrombin time >100 seconds or INR >6.5 or • Any three of the following: – Age >40 or <10 years – Prothrombin time >50 seconds or INR > 3.5 – Any grade of hepatic encephalopathy with jaundice to encephalopathy time >7 days – Serum bilirubin >300 mol/L (17.54 mg/dL)	
NHS criteria for unfavorable etiologies [seronegative hepatitis, idiosyncratic drug reactions, drug-induced liver injury (DILI), others]	• Prothrombin time >100 seconds or INR >6.5 or • In the absence of clinical hepatic encephalopathy – INR >2 after vitamin K repletion is mandatory and – Any two of the following - Age >40 years - Age <10 years - Prothrombin time >50 seconds or INR >3.5 • If hepatic encephalopathy is present – Jaundice to encephalopathy time >7 days – Serum bilirubin >17.54 mg/dL (>300 mmol/L)	

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Criteria, year, etiologies	*Prognostic parameters*	*Criteria performance*
Yellow phosphorus (rodenticide)	*Three of the following four criteria:* 1. Prothrombin time >100 seconds or INR >6.5 after vitamin K repletion. In patients undergoing plasmapheresis, 12 hours after the second set of plasmapheresis, if INR >2.5 2. MELD > 37 3. HE ≥ grade II 4. Arterial lactate (24 hours after admission) ≥6 mmol/L after fluid resuscitation No active cardiac dysfunction (EF <50%)	
AIH	Histology showing: • Confluent or massive hepatic necrosis (AIH/DILI) • Marked microvesicular steatosis (DILI) • Cholestatic hepatitis with ductopenia (DILI) MELD >28 No improvement in bilirubin/INR with steroids for 5 days	
Pediatric	Any one of the below: • INR >4 or • Grade 3–4 encephalopathy Multisystem disorders such as leukemia, lymphoma, hemophagocytosis, and disseminated intravascular coagulopathy are excluded	

(ALFSG: acute liver failure study group; ALFED: acute liver failure early dynamic; AIH: autoimmune hepatitis; BILE: Bilirubin Lactate and Etiology; DILI: drug-induced liver injury; EF: ejection fraction; HAV: hepatitis A virus; HBV: hepatitis B virus; HE: hepatic encephalopathy; HEV: hepatitis E virus; ICP: intracranial pressure; JEI: jaundice-encephalopathy interval; KCC: King's College Criteria; KCH: King's College Hospital; LT: liver transplantation; MELD: model for end-stage liver disease; NHS: National Health Service; INR: international normalized ratio; PT: prothrombin time)

- *Patients unlikely to survive without transplant:* Need urgent LT (prognostic models should have high sensitivity and specificity to predict death).
- *Patients with a high likelihood of spontaneous recovery and functionality with medical management*: Do not need LT.
- *Patients too sick to transplant*: LT is likely to be futile.

The decision for LT is often a dynamic one based on:

- Persistence of accepted ALF criteria is associated with a poor prognosis.
- Patients with sustained improvement in prognostic criteria and an absence of clinical deterioration should wait
- Patients with favorable etiologies such as paracetamol, HAV, HEV, and others have a good chance of spontaneous recovery
- Comorbidities and conditions independent of ALF that would impact survival, such as active infection, sepsis, invasive fungal infection, rapidly escalating inotropes, severe pancreatitis (usually in paracetamol-related ALF)
- Complications of ALF associated with reduced survival, especially compromised brainstem function, especially fixed and dilated pupils
- Psychosocial profile suggestive of poor adaptation of rigor of post-transplant survival
- Availability of a suitable donor for LT. Marginal livers from the elderly, steatotic, ABO incompatible, and others should preferably be avoided.

Most organ allocation systems prioritize ALF over CLD due to higher short-term mortality risk. Patients with Wilson's disease, AIH, or Budd–Chiari syndrome with ALF phenotype are also prioritized for LT despite having underlying CLD.

LIVER TRANSPLANTATION FOR ACUTE-ON-CHRONIC LIVER FAILURE

Acute-on-chronic liver failure is the syndrome of acute decompensation in a patient with CLD or cirrhosis characterized by rapidly progressive deterioration and high short-term mortality **(Table 8)**.

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Acute-on-Chronic Liver Failure: Definitions

A global consensus on the definition of acute-on-chronic liver failure has not yet been reached. Three definitions are most widely used; the APASL/AARC (Asian Pacific Association for the Study of the Liver/APASL ACLF Research Consortium) definition, which is followed in the regions of South East Asia and South Asia, the EASL-CLIF (European Association for the Study of the Liver—Chronic Liver Failure) definition, which is followed in Europe, and the North American Consortia for the Study of End-Stage Liver disease (NASCLED) definition, which is followed in North America. The key differences between the definitions are summarized in **Table 8**.

TABLE 8: Acute triggers for acute-on-chronic liver failure.

	APASL (Asian Pacific Association for the Study of the Liver)/AARC (APASL ACLF Research Consortium)	***EASL-CLIF (European Association for the Study of the Liver-Chronic Liver Failure)***	***NACSELD (North American Consortia for the Study of End-Stage Liver Disease)***
Definition	Acute hepatic insult manifesting as jaundice (total bilirubin ≥5 mg/dL) and coagulopathy (INR of ≥1.5, or prothrombin activity <40%) complicated by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed CLD associated with high mortality	Acute deterioration of pre-existing CLD is usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure	A syndrome characterized by acute deterioration in a patient with cirrhosis due to infection, presenting with two or more extrahepatic organ failures
Inclusion	• Compensated cirrhosis (diagnosed or undiagnosed) • CLD but not cirrhosis • Acute insult directed at the liver • Presentation with liver failure • Index presentation	• Cirrhosis (compensated or decompensated) • Renal failure is mandatory • Presentation is not necessarily associated with liver failure • Can be repeated episodes of ACLF	• Cirrhosis (compensated or decompensated) • Two extrahepatic organ failures • Presentation is not necessarily associated with liver failure • Can be repeated episodes of ACLF
Time frame	4 weeks	4–12 weeks (variable)	Not defined
Precipitating factors	Intrahepatic	Intrahepatic (alcoholic hepatitis), extrahepatic (infection, gastrointestinal bleed), or both	Extrahepatic (infection)
Major organ systems considered for definition	Liver	One of the six major organ systems (liver, kidney, brain, coagulation, circulation, and respiration)	Two to four organ systems (kidney, brain, circulation, and respiration)
Exclusion criteria for the absence of ACLF	• Acute decompensation of cirrhosis • Prior decompensation HCC	• HCC • No organ system failure • Single organ failure (liver, coagulation, circulation, respiration) without kidney or brain dysfunction • Cerebral failure without kidney dysfunction	• Infections not requiring hospitalization • Cirrhosis without infection • *Immune-compromised patients:* HIV, prior organ transplant, disseminated malignancies • None of the four organ failures used to define ACLF • Single organ system failure
Homogeneity	More homogeneous patients	Heterogeneous patients (40% have unknown acute insult), extrahepatic organ failure, and systemic inflammation may confound comparative studies	Heterogeneous patients, extrahepatic organ failure, and systemic inflammation may confound comparative studies

(ACLF: acute-on-chronic liver failure; CLD: chronic liver disease; HCC: hepatocellular carcinoma; HIV: human immunodeficiency virus; INR: international normalized ratio)

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Acute-on-Chronic Liver Failure Precipitants/Triggers

Acute-on-chronic liver failure is often triggered by identifiable acute events, with bacterial infections such as spontaneous bacterial peritonitis (SBP), secondary peritonitis, and pneumonia being the most common, in addition to alcohol and HBV exacerbation (few eastern countries) **(Table 9)**.

Prognostication and Indication for LT

Acute-on-chronic liver failure offers a very narrow therapeutic window for LT. The prognosis depends on the number of hepatic and extrahepatic organ failures. However, if infection is the trigger for ACLF, it may preclude an LT. Different scoring systems for the prognostication of ACLF are outlined in **Table 10**.

For patients not meeting the ACLF definition, the CLIF-C AD (acute decompensation) score is used for prognostication. The CLIF-C ACLF score of >65 is associated with 100% mortality in 3–7 days, and LT may be futile.

LIVER TRANSPLANTATION FOR LIVER TUMORS

Hepatocellular Carcinoma

Liver transplantation may be curative for liver cirrhosis with HCC since it removes the tumor with the widest possible margin and reduces the risk of new tumors. Most HCC patients have compensated cirrhosis or early decompensation and, therefore, have CTP/MELD scores. Since their mortality risk is dominantly determined by the progression of HCC rather than cirrhosis, criteria based on tumor characteristics are used for organ allocation. Milan and University of California San Francisco (USCF) criteria are most commonly used, although several other/expanded criteria have been described **(Table 11)**. Patients may require locoregional or systemic therapy to prevent tumor progression while waiting for a transplant (bridging) or to downstage them to within the criteria.

Cholangiocarcinoma

Cholangiocarcinoma (CCA) is an aggressive tumor with a poor prognosis. Radical surgical resection with clear

TABLE 9: Acute triggers for acute-on-chronic liver failure.

Triggers	*Common*	*Uncommon*
Infections	• Bacterial infections – Spontaneous bacterial peritonitis – Spontaneous bacterial empyema – Spontaneous/secondary bacteremia – Urinary tract infection – Pneumonia – Bronchitis – Skin and soft-tissue infection – Cholangitis – Secondary peritonitis – *Clostridium difficile* infection • Fungal infections – Invasive candidiasis – Invasive aspergillosis • Hepatotropic viral infections – Hepatitis B virus (HBV) infection or reactivation – Superimposed hepatitis A – Superimposed hepatitis E	• Hepatotropic viral infections – Superimposed hepatitis D in patients with chronic HBV – Superimposed hepatitis C • Systemic viral infections – Epstein–Barr virus (EBV) – Cytomegalovirus (CMV) – Herpes simplex virus (HSV 1, 2, 6) – Varicella zoster virus (VZV) – Human immunodeficiency virus (HIV) – Parvovirus B19 – Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – Influenza A, influenza B, and syncytial respiratory virus • *Parasitic infection:* Visceral Leishmaniasis
Toxin/drugs	• Alcoholic hepatitis • Drug-induced acute kidney injury • Drug-induced encephalopathy	Drug-induced liver injury (DILI)
Others	Gastrointestinal hemorrhage ± shock	• Wilson's disease • Flare of autoimmune hepatitis (AIH) • Ischemic hepatitis • Surgical or radiological intervention

Note: 20–40% of cases have no identifiable trigger, possibly linked to bacterial translocation or hepatocyte damage.[46]

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