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The Kidney and Extracorporeal Therapies in Acute-on-Chronic Liver Failure: What the Nephrologist Needs to Know

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ABSTRACT

In this review, we discuss the pathophysiology and management of acute kidney injury (AKI) in the setting of acute-on-chronic liver failure (ACLF). ACLF is characterised by the occurrence of acute hepatic and/or extrahepatic organ failure, induced by immune dysregulation and systemic inflammation in patients with chronic liver disease. Kidney involvement is common, with AKI occurring in 30% to > 95% of ACLF patients, depending on the definition used. Since there is a lack of kidney biopsy data in these patients, the underlying pathophysiological basis of AKI remains incompletely understood, and systemic inflammation is believed to be the primary driver of organ injury. The management of AKI has been largely extrapolated from studies in decompensated cirrhosis, and there is little data specifically in the ACLF setting. However, available evidence suggests that structural kidney injury is more common in ACLF than in decompensated CLD, and therefore, AKI in ACLF is less likely to respond to volume repletion and vasopressors. Treatment options remain limited for those who are non-responsive to intravenous fluids and vasopressors. Liver transplantation (LT), with or without kidney transplantation, is the definitive treatment for these patients. At present, extracorporeal therapies such as therapeutic plasma exchange and kidney replacement therapies play a supportive role in ACLF as a bridge to LT; however, the optimal timing and dosing remain unclear. While theoretically, extracorporeal therapies have the potential to reverse or halt progression of organ damage in ACLF, there is limited evidence currently.

1 | Introduction

Acute-on-chronic liver failure (ACLF) is characterised by acute, severe liver injury and multiorgan failure due to an acute insult in a patient with chronic liver disease (CLD) or cirrhosis. While multiple definitions of ACLF exist, the Asian Pacific Association for the Study of the Liver (APASL) and European Association for the Study of Liver (EASL) definitions are the most widely used (Figure 1) [1, 2]. The kidney is the most common extrahepatic organ that is involved in ACLF, with acute kidney injury (AKI) occurring in 30% to > 95% of patients, depending on the definition of ACLF [3–7]. The phenotype of AKI in ACLF has been described to be considerably different from that in decompensated cirrhosis, with the former being less likely to be fluid- or terlipressin-responsive, more severe with a greater risk of kidney replacement therapy requirement (KRT) and more likely to have structural kidney damage [8, 9]. The presence of AKI in a patient with ACLF also has adverse prognostic implications and is associated with a 28-day mortality of as high as 50% [9, 10]. AKI also adversely impacts liver transplantation outcomes in ACLF patients [1, 11–13]. These considerations make the role of a

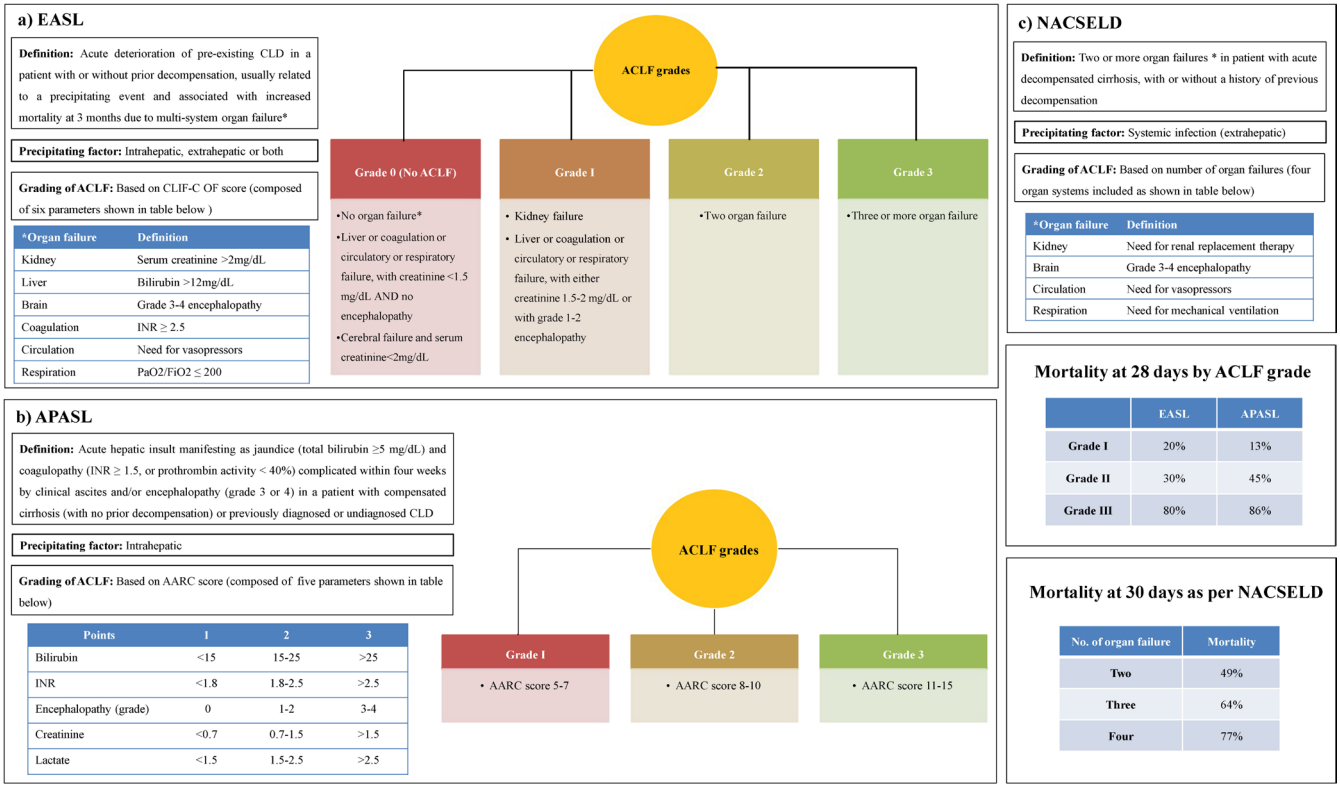

FIGURE 1 | Comparison of the EASL, APASL and NACSELD definitions and grading of ACLF. Created with BioRender.com. AARC, APASL-ACLF research consortium; ACLF, acute on chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; CLD, chronic liver disease; CLIF-C OF, chronic-liver-failure consortium organ failure; EASL, European Association of Study of Liver; INR, international normalised ratio; NACSELD, North American consortium for the study of end-stage liver disease.

nephrologist integral to the management of ACLF patients, and a thorough understanding of liver-kidney crosstalk and management strategies is key to improving patient outcomes.

In recent years, there has been a growing understanding about the pathophysiology and prognostic implications of AKI in ACLF, and this has led to the reassessment of diagnostic criteria and management strategies in these patients. In this review, we describe the current understanding of the pathophysiology of AKI in ACLF and its management, including the role of extracorporeal therapies. Our search strategy for this review involved a PubMed database search to identify studies published between 1st January 2001 to 31st March 2024, using a combination of the following search terms: “acute-on-chronic liver failure,” “ACLF,” “kidney,” “renal,” “hepatorenal,” “extracorporeal,” “plasmapheresis,” “dialysis” and “transplant.”

2 | Pathophysiology of AKI in ACLF

The pathogenesis of AKI (and other organ dysfunction) in ACLF has been described to be primarily due to systemic inflammation and may involve one or more of three pathways: direct cellular damage by immune cells, tissue hypoperfusion due to endothelial activation and microvascular thrombi, and competition for nutrients and ATP by inflammatory cells leading to peripheral organ hypometabolism [14]. This systemic inflammation may be initiated by bacterial infection or by translocation of bacteria (or their products) from the intestinal lumen [15–18]. This leads to elevated levels of pathogen-associated molecular patterns (PAMPs) such as bacterial nucleic acids and lipopolysaccharide in the systemic circulation causing activation of innate immunity via pattern recognition receptors (PRPs) (Figure 2). Pro-inflammatory cytokines, chemokines, and adhesion molecules are then released leading to renal vasoconstriction and structural damage in the form of acute tubular necrosis (ATN). The release of damage-associated molecular patterns (DAMPs) from damaged hepatocytes also induces a similar systemic inflammatory response. This was demonstrated by Sole et al. who found that the levels of several inflammatory cytokines were elevated in patients with ACLF compared to those with cirrhosis without ACLF [16].

Hemodynamic alterations due to portal hypertension leading to hepatorenal syndrome (HRS) are another potential mechanism of AKI. An increase in portal pressure causes the release of endogenous vasodilators like nitric oxide that results in splanchnic vasodilation and a decrease in the effective arterial blood volume. This activates the renin-angiotensin-aldosterone (RAS) pathway and the sympathetic system, thereby leading to renal vasoconstriction, reduced renal perfusion, and a reduced glomerular filtration rate. Although earlier it was believed that HRS occurs exclusively in the presence of cirrhosis with ascites, it is now accepted that HRS can occur even in patients with ACLF and acute liver failure [4].

Bile cast nephropathy (BCN), also called cholemic nephropathy, is another cause of AKI in the setting of severe

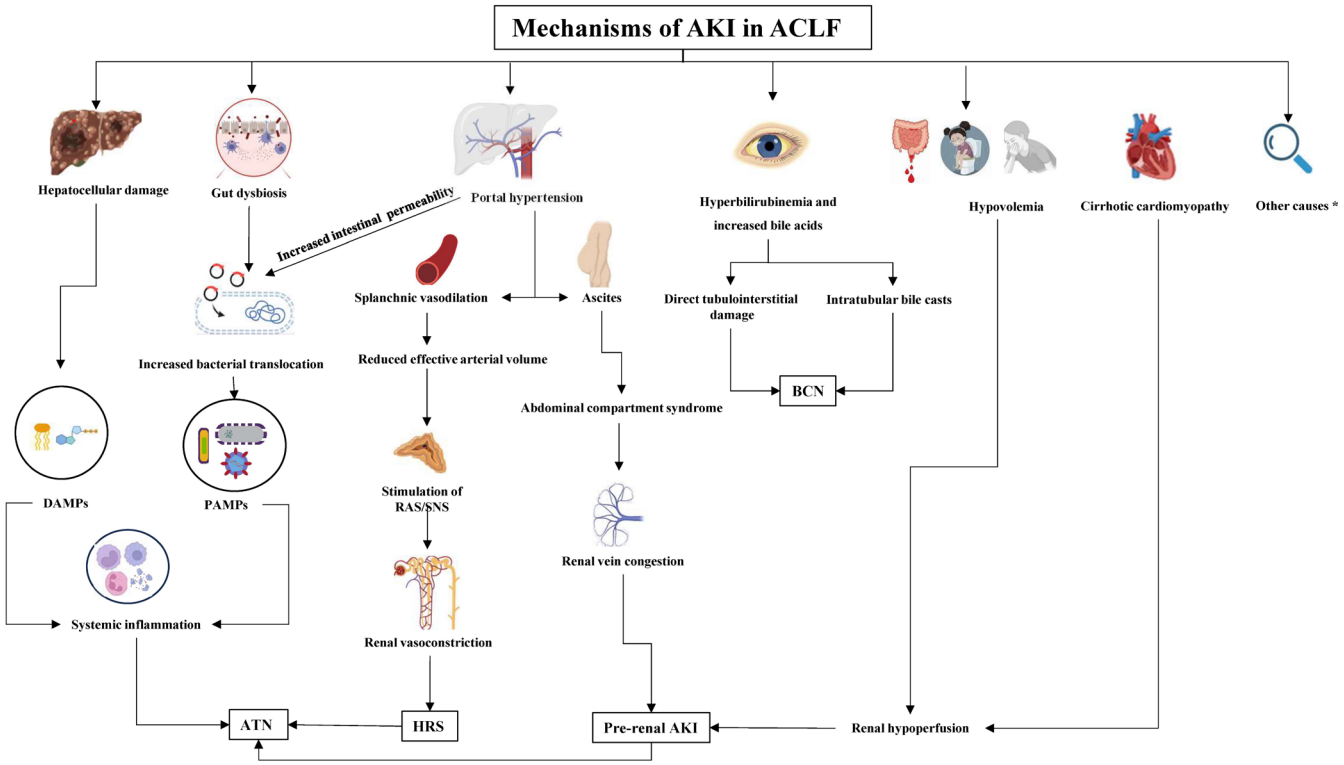

FIGURE 2 | Mechanisms of AKI in ACLF. Created with BioRender.com. ACLF, acute on chronic liver failure; AKI, acute kidney injury; ATN, acute tubular necrosis; BCN, bile cast nephropathy; DAMPs, damage-associated molecular patterns; HRS, hepatorenal syndrome; PAMPs, pathogen-associated molecular patterns; RAS, renin-angiotensin-aldosterone; SNS, sympathetic nervous system.

hyperbilirubinemia. It has been demonstrated that high urinary levels of bilirubin and bile acids can cause tubulointerstitial inflammation and fibrosis due to direct tubular epithelial cell toxicity or lead to the formation of intratubular bile casts and obstruction leading to kidney injury [19, 20]. Although underdiagnosed and underreported due to the lack of kidney biopsy data, this entity may be one of the most common causes of AKI in the ACLF setting. Nayak et al., in an analysis of post-mortem kidney biopsies, found that 72.1% of patients with ACLF and a diagnosis of HRS-AKI at admission had BCN [21]. Another post-mortem study of kidney biopsies of patients with ACLF and stage 3 AKI found that BCN was the most common finding (seen in 54%), followed by ATN in 31% and a combination of BCN and ATN in 15% [22].

Cirrhotic cardiomyopathy is a condition characterised by systolic and diastolic dysfunction and electrophysiologic abnormalities in the absence of an underlying cardiac disease and is reported to occur in as high as 60% of patients with cirrhosis [23]. Since this entity manifests clinically under stress conditions, these abnormalities are more marked in ACLF and contribute to pre-renal AKI and ischemic ATN. Paracentesis-induced circulatory dysfunction (PICD) is a condition that has been reported in cirrhotic patients undergoing large volume paracentesis (> 5 L of ascitic fluid) and is characterised by an acute reduction in the systemic vascular resistance, decreased effective intravascular volume and RAS activation. It is associated with a more rapid re-accumulation of ascites, hyponatremia, hepatic encephalopathy, AKI and poor survival [24]. In the setting of ACLF, PICD may occur in up to 70% even with modest-volume paracentesis (< 5 L) and may contribute to the occurrence of AKI [25].

Gastrointestinal haemorrhage, diarrhoea, and aggressive use of diuretics can lead to reduced intravascular volume, renal hypoperfusion, and an acute reduction in glomerular filtration rate (functional AKI) without any structural kidney injury. However, a prolonged pre-renal insult and resultant renal hypoperfusion can eventually lead to ATN. Raised intra-abdominal pressure due to tense ascites can cause intra-abdominal hypertension, renal vein congestion, and consequent AKI. Other causes of AKI include drug-induced ATN or interstitial nephritis, glomerulonephritis, obstructive uropathy, and intrinsic renal diseases due to concurrent comorbid illnesses.

3 | Medical Management of AKI in ACLF

3.1 | General Approach to Management

A multipronged approach is needed to manage AKI in ACLF, with prompt identification and treatment of the acute insult, withdrawal of diuretics, avoidance of nephrotoxic medications and contrast media, prevention of sepsis, and treatment of organ failure (Figure 3). In patients with cirrhosis and septic shock, targeting a higher mean arterial pressure (MAP) of 80–85 mm Hg has been found to be associated with improved renal outcomes, compared to a target MAP of 60–65 mm Hg; however, no survival benefit has been found and there may be

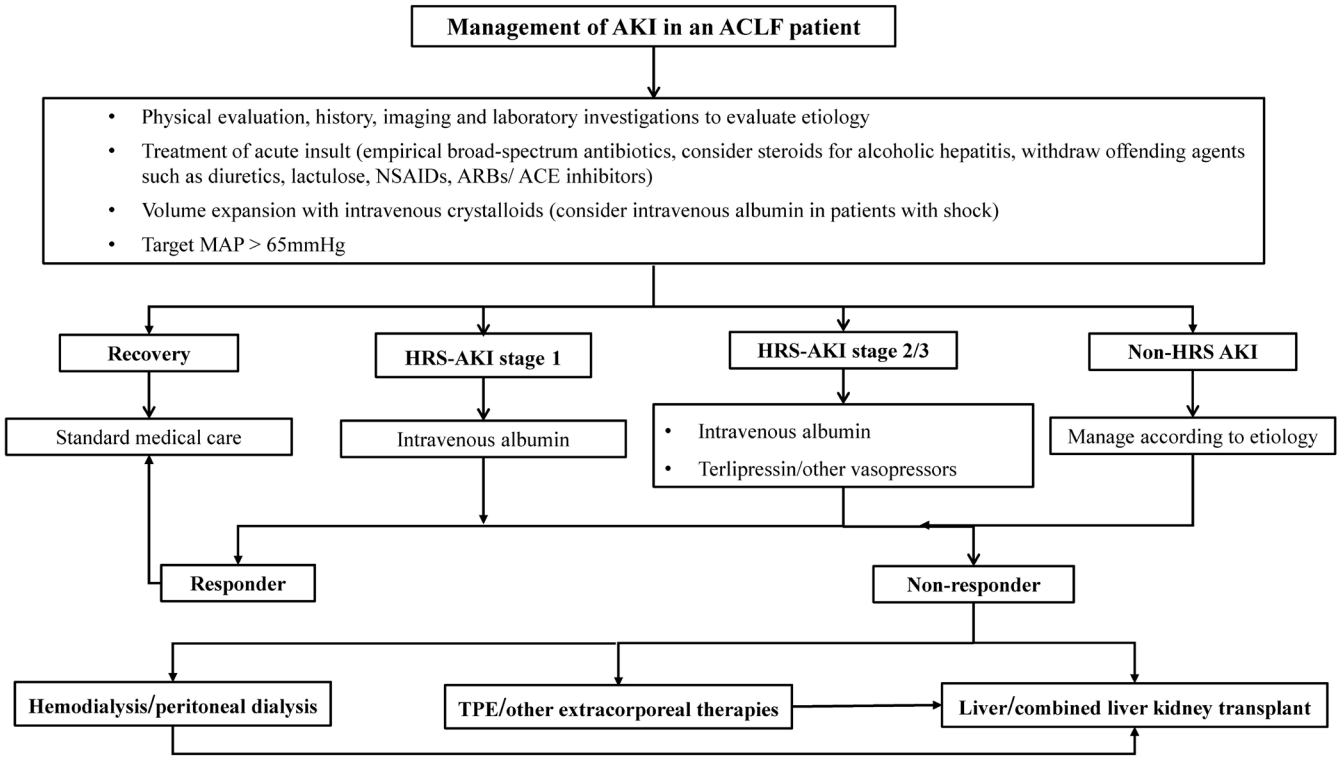

FIGURE 3 | Management of AKI in an ACLF patient. ACE, angiotensin-converting enzyme; ACLF, acute on chronic liver failure; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; HRS, hepatorenal syndrome; MAP, mean arterial pressure; NSAIDs, nonsteroidal anti-inflammatory drugs; TPE, therapeutic plasma exchange.

a higher risk of adverse events [26]. Pre-renal AKI is suspected when patients with ACLF present with features of hypovolemia, with a history of vomiting, diarrhoea, GI bleed etc. Persistent or progressive AKI despite intravascular volume repletion should prompt a diagnosis of HRS-AKI when the other diagnostic criteria are met (Table 1) and necessitates early initiation of vasopressors [4, 6]. While previous definitions of HRS-AKI included serum creatinine alone, newer definitions have incorporated urine output criteria too, recognising the fact that oliguria is a sensitive marker of AKI and is associated with higher mortality in cirrhosis [27]. Further, the pre-requisite for administration of albumin for 48 h before making a diagnosis of HRS-AKI has been removed from the 2024 definition, since this requirement may unnecessarily delay initiation of vasopressor therapy [6]. Patients who do not meet the criteria of HRS-AKI are considered to have non-HRS AKI, and management depends on the underlying aetiology. The presence of bile casts on urinalysis should raise a suspicion of BCN. Acute tubular necrosis (ATN) can be considered if there is shock or a history of intake of nephrotoxic drugs, urinary osmolality < 400 mOsm/L, urinary sodium > 40 mEq/L and fractional excretion of sodium (FeNa) > 2% [28].

It is important to note that current diagnostic criteria do not always differentiate between HRS-AKI and non-HRS AKI. It should also be noted that although the pathogenetic mechanisms are different, there is considerable overlap between the two entities, and HRS-AKI may evolve to non-HRS AKI in some cases. There may be a role of biomarkers in this regard, although further studies are warranted in the ACLF setting [6, 29]. In patients with decompensated cirrhosis, it has been found that urine NGAL levels may have a role in distinguishing between HRS-AKI and ATN; however, there are no universally accepted cut-off values at present [30–33]. In an analysis of 12 urinary biomarkers in 55 patients with decompensated cirrhosis (of which 62% had ACLF), Ariza et al. found that the biomarkers with the highest accuracy for a diagnosis of ATN (vs. other causes of AKI) were NGAL (AUC 0.96), followed by interleukin-18 (IL-18) (AUC 0.92), albumin (AUC 0.86), trefoil-factor-3 (TFF-3) (AUC 0.82), and glutathione-S-transferase-π (AUC 0.81) [30]. The definitive test to identify the cause of AKI, however, is kidney biopsy, but this is generally not feasible in the ACLF setting due to accompanying thrombocytopenia and/or coagulopathy. Those who do not respond to vasopressor therapy should be considered for extracorporeal therapies or liver transplantation (either alone or in combination with kidney transplantation).

3.2 | Role of Intravenous Albumin

Administration of intravenous albumin (at a dose of 1 mg/kg/day of 20%–25% albumin, up to 100 g/day for 2 days) is recommended for volume expansion in patients with ACLF and AKI [29]. Albumin may also have beneficial effects through its protective effect on the endothelium, and its immunomodulatory and antioxidant properties [34–36]. The 2024 APASL guidelines recommend that, unlike in decompensated cirrhosis, albumin be initiated even in patients with stage 1 AKI [29]. Further, in ACLF patients with AKI and shock, the use of 4%–5% albumin has been recommended over crystalloids [29].

Although albumin alone may have a limited role in HRS–AKI, the addition of albumin to terlipressin has been demonstrated

TABLE 1 | Revised definition and classification of HRS.

New terminology	Old terminology	Criteria
HRS	—	ICA 2019 definition [4] 1. Presence of cirrhosis, acute liver failure or acute-on-chronic liver failure 2. AKI defined as follows: Rise in serum creatinine by ≥ 0.3 mg/dL within 48 h, or ≥ 50% increase from baseline values and/or Urine output ≤ 0.5 mL/kg/h for at least 6 h 3. Lack of response after at least 2 days of diuretic withdrawal and volume expansion with albumin (at a dose of 1 g/kg/day, max. 100 g/day) 4. Absence of shock 5. Absence of current/recent use of nephrotoxic drugs 6. Absence of kidney parenchymal damage (in patients with no pre-existing chronic kidney disease) as suggested by significant proteinuria (> 500 mg/day), microscopic hematuria (> 50RBCs/hpf), biomarkers of kidney injury, and/or abnormal kidney ultrasound ICA-ADQI 2024 definition [6] 1. Cirrhosis with ascites 2. AKI, defined by an increase in serum creatinine by ≥ 0.3 mg/dL within 48 h or ≥ 50% from baseline values that is known or presumed to have occurred within the last 7 days and/or urine output of ≤ 0.5 mL/kg for ≥ 6 h 3. No improvement in AKI within 24 h after adequate volume resuscitation 4. No alternative primary cause for AKI
HRS-AKI	Type 1 HRS	(a) Absolute increase of serum creatinine by > 0.3 mg/dL within 48 h, or > 1.5-times increase in serum creatinine from baseline values within last 7 days and/or (b) Urine output < 0.5 mL/kg for at least 6 h
HRS-non-AKI (HRS-NAKI)		
• HRS-AKD	Type 2 HRS	(a) eGFR < 60 mL/min/1.73m^2 for < 3 months in the absence of other causes or (b) Increase in serum creatinine by < 50% from baseline values within last 3 months
• HRS-CKD		eGFR < 60 mL/min/1.73m^2 for at least 3 months in the absence of other causes

Abbreviations: AKI, acute kidney injury; HRS, hepatorenal syndrome; HRS-AKD, hepatorenal syndrome acute kidney disease; HRS-AKI, hepatorenal syndrome-acute kidney injury; HRS-CKD, hepatorenal syndrome chronic kidney disease; HRS-NAKI, hepatorenal syndrome non-acute kidney injury; RBC, red blood cells.

to markedly increase response rates, compared to terlipressin alone (77% vs. 25%) [37, 38]. Therefore, concomitant use of albumin beyond the initial volume resuscitation phase has been recommended at a dose of 20–40 g/day (until resolution of AKI or for a maximum of 14 days), along with vasopressor therapy [39–42]. However, excessive use of albumin should be avoided since it can have detrimental effects. A recent RCT found that in patients with decompensated cirrhosis, repeated daily intravenous albumin targeting a serum albumin of ≥ 3 g/dL does not improve outcomes as compared to standard care and is, in fact, associated with higher serious adverse events, specifically volume overload and lung infections [43].

The role of intravenous albumin in the prevention of PICD in cirrhosis undergoing large volume paracentesis (> 5 L) is already known [41]. Further, a recent RCT found that albumin (8 g for every dL of ascitic fluid) improves 28-day survival and prevents PICD and AKI in ACLF patients undergoing modest volume (< 5 L) paracentesis [25].

In cirrhotic patients with spontaneous bacterial peritonitis (SBP) (especially those with a serum bilirubin ≥ 4 mg/dL or creatinine ≥ 1 mg/dL), co-administration of albumin (1.5 g/kg at diagnosis, followed by 1 g/kg on day 3) and antibiotics has been found to reduce AKI and mortality risk, compared to antibiotics alone [44].

There is no evidence, however, to support the use of albumin in non-SBP infections [29, 41].

3.3 | Terlipressin and Other Vasopressors

Terlipressin is a non-selective synthetic vasopressin analogue that causes splanchnic vasoconstriction, thus reducing portal hypertension, and improving effective arterial blood volume and renal perfusion through its effect on the vasopressin V1 receptor [45]. It has been used as either repeated intravenous boluses (0.5–2 mg every 6 h) or as a continuous infusion (2–12 mg/day), and while both have been demonstrated to have similar efficacy, continuous infusion is better tolerated and is therefore preferred [46]. It has proven efficacy for HRS-AKI reversal and reduction of short-term mortality in decompensated cirrhosis, though not currently approved by the US Food and Drug Administration [45, 47, 48]. However, there is limited data available in the ACLF setting. While Jindal et al. reported that just over a third of patients with ACLF and HRS respond to terlipressin, higher response rates of 53%–65% have been reported by others [7, 49, 50]. It has been reported that the response rate to terlipressin decreases with increasing grade of ACLF, from 60% in grade 1 ACLF to 29% in grade 3 ACLF [51]. Baseline serum creatinine was another significant predictor of response in this study, highlighting the need for early diagnosis and treatment [51]. The recently published "Early Versus Standard Initiation of Terlipressin for Acute Kidney Injury in ACLF: A Randomized Controlled Trial (eTerli study)" compared the effect of early terlipressin (given as a continuous infusion at 2 mg/day) plus 20% albumin (20-40 g/day) versus standard therapy (intravenous 20% albumin for 48 h, followed by terlipressin plus albumin) in 70 ACLF patients with stage II/III AKI not responding to albumin infusion at 12 h. A higher rate of HRS reversal (68.6% vs. 31.4%; $p = 0.03$) and lower 28-day mortality (40% vs. 65.7%, $p = 0.031$) was found in the early terlipressin group [52]. Concern remains, however, about its safety, with a reported 21%–46% developing adverse effects such as diarrhoea, abdominal pain, intestinal or peripheral ischemia, and angina [49, 50]. An association with respiratory failure has also been reported in patients with advanced liver disease [53]. Therefore, terlipressin should be used with caution in patients with cardiovascular disease and grade 3 ACLF.

Noradrenaline is an alternate option in ACLF patients with HRS-AKI. It primarily acts by causing vasoconstriction through α-adrenergic receptors and thereby improving renal perfusion. Arora et al., in a RCT of 120 patients with ACLF and HRS, found that those who received terlipressin had higher HRS reversal (40% vs. 16.7%) and lower KRT requirement (56.6% vs. 80%). The 28-day survival was also higher in the terlipressin group (48.3% vs. 20%) [54]. Adverse events were higher in the terlipressin group (23.3% vs. 8.3%), although they were reversible [54]. A recent systematic review and meta-analysis, however, reported that although HRS reversal and one-month survival were numerically higher with terlipressin compared to noradrenaline, this was not statistically significant [55]. Midodrine (in combination with octreotide) has also been used in AKI-HRS; however, it is inferior to terlipressin in decompensated cirrhosis, and there are no studies in the ACLF setting [56].

The 2024 APASL guidelines recommend continuous infusion of terlipressin as the vasoconstrictor of choice in patients with ACLF and HRS-AKI [29]. If there is no improvement in urine output (to > 0.5 mL/kg/h) or reduction of serum creatinine by at least 25% by day 3, the dose is increased in a stepwise manner. Patients in whom these targets are not achieved, despite the maximum tolerated dose of terlipressin, are considered non-responders [29]. In these cases, the drug is discontinued, and alternative therapies should be considered. It is important to note that lack of response to terlipressin predicts a higher risk of 90-day mortality [50, 51].

4 | Kidney Replacement Therapy (KRT) in ACLF

There is insufficient evidence at present about the optimal timing of dialysis in ACLF. Dialysis is indicated as an urgent intervention in patients with AKI and life-threatening complications such as uremic encephalopathy, pulmonary edema, severe metabolic acidosis, severe hyperkalemia, and advanced azotemia [57]. However, the role of early dialysis (initiation of dialysis in the absence of urgent indications) is unclear [57, 58]. A recent RCT of ACLF patients with septic shock and AKI reported higher renal recovery and a trend toward improved 28-day survival with early initiation of continuous kidney replacement therapy (CKRT) [52]. The 2024 APASL guidelines recommend that KRT be considered in patients with ACLF with Stage 3 AKI who progress or do not respond to vasoconstrictor therapy within 12–24 h [29].

CKRT is the preferred modality of dialysis in this population since it is associated with better hemodynamic stability, slower correction of hyponatremia and lower risk of increased intracranial pressure, although there is no robust evidence for its superiority over intermittent haemodialysis (IHD), sustained low-efficiency dialysis (SLED) or peritoneal dialysis (PD) in terms of improved survival or renal outcomes [57, 59]. In resource-limited settings where CKRT is unavailable, SLED has been used as an alternative. Although a study by Ponce et al. found that adequate solute and volume control can be achieved with PD in ACLF patients, it remains an underutilised modality [60].

In patients with ACLF requiring KRT, anticoagulation is challenging and demands a meticulous balancing act to prevent clotting of the extracorporeal circuit without leading to bleeding complications. The various anticoagulation methods available are outlined in (Table 2). In critically ill patients on CKRT, regional citrate anticoagulation (RCA) is the anticoagulation of choice due to its association with longer circuit survival times and lower bleeding risks [61, 62]. however, in patients with ACLF, the use of RCA is controversial due to reduced hepatic metabolism of citrate and risk of citrate toxicity, manifesting as metabolic acidosis, a high total calcium (Ca_{tot}) to ionised calcium (Ca_i) ratio (Ca_{tot}/Ca_i), arrhythmias and haemodynamic instability [63, 64]. Pharmacokinetic studies have shown that citrate clearance in ACLF may be impaired by 75%, in comparison to other critically ill patients [63]. A systematic review of 10 observational studies found that the pooled incidence of citrate accumulation was 12% in liver failure patients receiving RCA for CKRT; however, there was no significant difference in the pH, serum lactate and Ca_{tot}/Ca_i ratio between those with and

TABLE 2 | Anticoagulants in ACLF.

Drug	Advantages	Disadvantages
Unfractionated heparin (UFH)	Less expensive, widely used, reversible, shorter half-life, easy monitoring (aPTT or ACT)	Unpredictable and complex pharmacokinetics that necessitates aPTT/ACT monitoring, risk of bleeding, HIT, heparin resistance due to low antithrombin levels
Regional citrate anticoagulation (RCA)	Low bleeding risk, lower risk of filter clotting in CKRT compared to UFH	Risk of citrate accumulation and toxicity may be particularly high in patients with severe liver failure, needs monitoring of calcium levels, limited data in IHD- higher blood and dialysate flow rates may make use of RCA complex
Low-molecular-weight heparin (LMWH)	Lower risk of HIT, more reliable anticoagulation	Expensive, cumulative effect, needs anti-Xa monitoring which is not readily available, limited data on safety and efficacy in AKI and liver failure
Saline dialysis	Eliminates bleeding risk	Limited efficacy in preventing dialysis circuit clotting
CKRT in predilution mode	Eliminates bleeding risk	Limited efficacy in preventing dialysis circuit clotting, reduces solute clearance, expensive
Others {direct thrombin inhibitors, heparinoids, danaparoid, UFH with protamine reversal (regional heparin), nafamostat maleate, heparin-coated hemofilters}	Limited data on safety and efficacy	

Abbreviations: ACLF, acute on chronic liver failure; ACT, activated clotting time; AKI, acute kidney injury; aPPT, activated partial thromboplastin time; CKRT, continuous renal replacement therapy; HIT, heparin-induced thrombocytopenia; IHD, intermittent haemodialysis.

without liver failure [65]. While further evidence from RCTs is warranted before the routine use of RCA can be recommended in this population, available evidence suggests that RCA may be used in ACLF patients under close monitoring [29, 66].

5 | Other Extracorporeal Liver Support Systems (ELSS)/Artificial Liver Support Systems (ALSS)

In ACLF patients who do not respond to albumin and vasopressors, other extracorporeal techniques have also been tried. These may act as a bridge to liver transplant (LT) or help improve patient or renal outcomes when LT is not an option. Several modalities have been tried including therapeutic plasma exchange (TPE), extracorporeal albumin dialysis (ECAD) and hemadsorption (Table 3); however, there is a lack of data in ACLF specifically.

5.1 | Therapeutic Plasma Exchange (TPE)/ Plasmapheresis

TPE has been used for the management of acute liver failure (ALF) since the 1990s. Its efficacy has been attributed to the removal of cytokines, replacement of plasma factors, and its immunomodulatory effects. Although high-volume TPE has been advocated by the 2016 EASL clinical practice guidelines as a level 1 recommendation for ALF, there is no evidence-based guidance for TPE in the ACLF setting [67]. A propensity-matched retrospective analysis of 1151 patients with ACLF found that 30-day mortality was lower in the TPE arm (21% vs. 50%), compared to standard care [68]. Further, Qui et al., in an RCT of 234 patients with HBV-related ACLF, found that those who received TPE had significantly higher 3-year (60% vs. 47%) and 5-year (43% vs. 31%) cumulative survival rates, compared to those on standard therapy [69]. A recent systematic review and meta-analysis of studies also found that TPE improved 30- and 90-day survival in ACLF patients who did not undergo liver transplantation [70]. Further, a retrospective study found that serum creatinine normalised in six of 10 patients treated with a combination of low-dose TPE and low-dose steroids [71]. Further studies are required to elucidate the role of TPE in the management of ACLF and its effect on kidney function.

5.2 | Hemoperfusion/Hemoadsorption

The CytoSorb cytokine adsorber is an approved medical device that effectively removes hydrophobic molecules in the 5–55 kDa range by hemoadsorption [72]. Although it has obvious

TABLE 3 | Summary of extracorporeal (or artificial) liver support systems used in ACLF.

ELSS type	Equipment	Dosing	Remarks
PLEX	Centrifugal techniques are more commonly used than membrane filtration	2–3 times/week continued till clinical improvement, liver transplant or death; exchange volume 1–2 times plasma volume (standard PLEX) or 0.5 times plasma volume (low volume PLEX)	• Widely available • Has been studied predominantly in the setting of HBV-related ACLF • No data on high volume PLEX (exchange volume of 4 times plasma volume) in ACLF
SPAD	Conventional KRT equipment	6-8 h; albumin concentration of 3%–4% in dialysate with dialysate flow rates of 700–1000 mL/h	• Can be performed using conventional haemodialysis machines—simpler set-up • Needs high volumes of exogenous albumin since spent albumin is discarded
MARS	Conventional KRT machine with MARS treatment kit	Up to 10 sessions for 6–8 h; blood flow rate 150–250 mL/min, albumin flow rate of 250 mL/min	• Most commonly used ECAD modality • Needs exogenous albumin, but lower volumes than for SPAD since spent albumin is recycled • High risk of circuit clotting – needs anticoagulation • Risk of hypotension
FPSA	Prometheus device (primary circuit with a high cut-off filter and a secondary circuit with two charcoal-based adsorption columns that remove albumin-bound toxins)	Five sessions in the first week, followed by three treatments in the second week (additional 3 treatments over third week if no clinical improvement); 4 h each	• Does not need exogenous albumin • Requires specialised equipment • Limited availability in LMICs • Circuit clotting and hypotension are main concerns as with MARS
DIALIVE	Dialysis machine connected to a high cut-off filter (Septex, Baxter) that removes albumin-bound toxins and cytokines, and a second filter that adsorbs DAMPS and PAMPS (Oxiris, Baxter)	Minimum of 3 sessions; 8–12 h each	• Has been studied in alcohol-related ACLF • Limited evidence available so far
CytoSorb	CytoSorb device (in prefilter position) used along with CKRT	Up to 72 h (CytoSorb device to be replaced at 8–24 h intervals)	• Limited evidence available so far
DPMAS	Uses a plasma filter and two specialised cartridges- HA 330II (neutral microporous resin) and BS 330 (anion exchange resin) that remove inflammatory mediators and bilirubin, respectively	Three sessions at 2- to 3-day intervals, along with low-volume PLEX; 4–4.5 h each	• Done in isolation, DPMAS can lead to loss of albumin and coagulation factors; hence, it is combined with PLEX • Has been studied predominantly in the setting of HBV-related ACLF • Available studies have predominantly focused on patients of Chinese ethnicity

Abbreviations: ACLF, acute-on-chronic liver failure; CKRT, continuous kidney replacement therapy; DAMPS, damage-associated molecular patterns; DPMAS, double plasma molecular adsorption system; ELSS, extracorporeal liver support system; FSPA, fractionated plasma separation and adsorption; KRT, kidney replacement therapy; MARS, molecular adsorbent recirculating system; PAMPS, pathogen-associated molecular patterns; PLEX, plasma exchange.

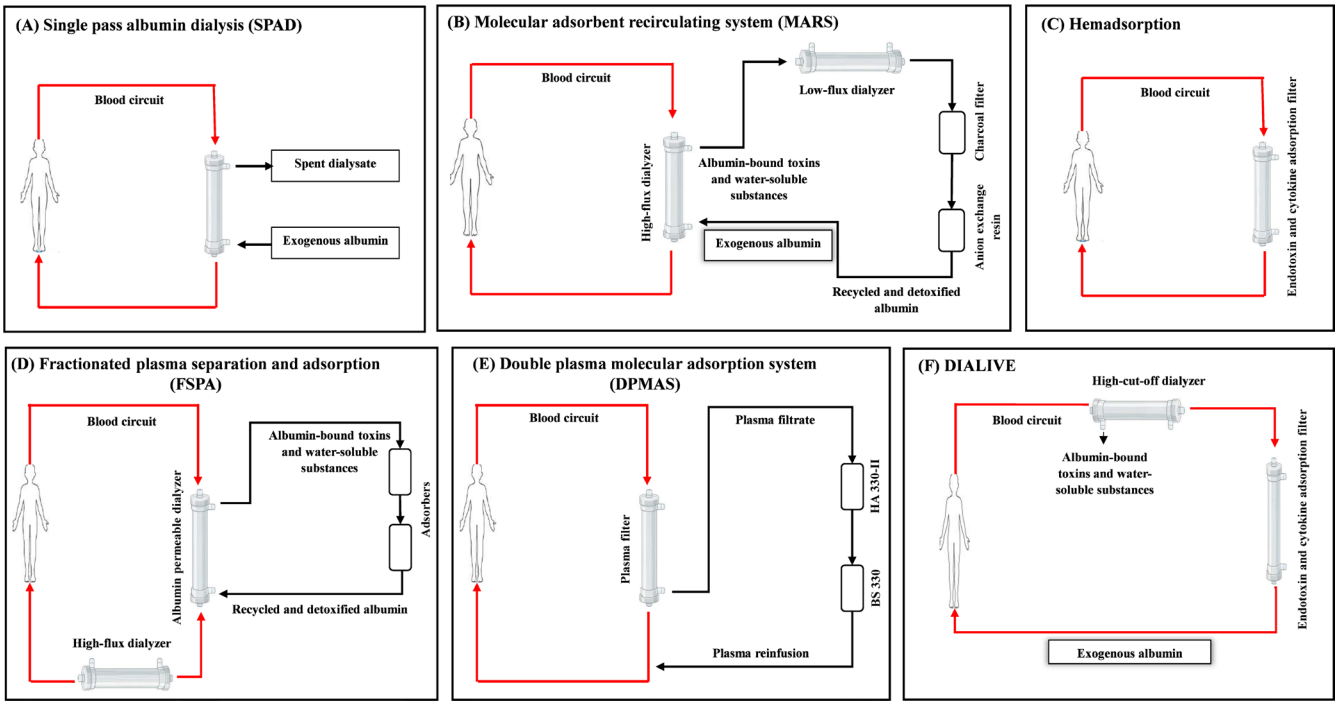

FIGURE 4 | Extracorporeal therapies in ACLF. Created with BioRender.com. ACLF, acute on chronic liver failure.

theoretical applications in ACLF through its potential to remove pro-inflammatory cytokines and bilirubin, robust evidence is lacking [73, 74].

Double plasma molecular adsorption system (DPMAS) is another haemoperfusion technique (Figure 4) that uses a plasma filter and two specialised cartridges-one with a neutral microporous resin (HA 330 II) and the other with an anion exchange resin (BS 330) that remove inflammatory mediators and bilirubin, respectively [75, 76]. In a propensity-matched study, patients with HBV-related ACLF, Wang et al. found that the 28-day survival was higher in those who received combined DPMAS and low-volume PLEX, in addition to standard treatment, compared to those who received standard treatment alone (97.9% vs. 85.4%, $p = 0.027$); however, this survival advantage was not sustained at 12 weeks (85.4% vs. 83.3%, $p = 0.687$) [77]. DPMAS combined with PLEX has been found to be superior (in terms of 28-day survival rates) to either DPMAS or PLEX alone in mild ACLF, but not in moderate and severe ACLF [78].

5.3 | Extracorporeal Albumin Dialysis (ECAD)

Based on the understanding that most toxins associated with liver failure are albumin-bound, hydrophobic molecules, extracorporeal techniques that use albumin to enable clearance of toxins have been used. Three different types of ECAD techniques have been described, namely, single-pass albumin dialysis (SPAD), molecular adsorbent recirculating system (MARS), and fractionated plasma separation and adsorption (FPSA) (Figure 4). Though these devices are not designed specifically for improving kidney outcomes, Mitzner et al. found that serum creatinine and one-month mortality were significantly lower in patients with HRS Type 1 treated with MARS, standard care, and hemodiafiltration than in patients receiving only standard care and hemodiafiltration [79]. The RELIEF trial too found that MARS dramatically reduced serum creatinine (percent change from baseline −20.04% vs. −6.43%) at Day 4, compared to standard care in patients with ACLF, although there was no improvement in 28-day survival [80]. On the other hand, Wong et al. found that in patients with cirrhosis, refractory ascites, and type 1 HRS who are non-responsive to vasoconstrictors, MARS does not improve systemic hemodynamics and renal function [81]. The HELIOS study randomised 145 patients with ACLF to either FPSA with the Prometheus device or standard care and found that although there was no difference in the 28-day or 90-day survival between the two arms, in the subgroup of patients with HRS Type 1, 28-day and 90-day survival was higher in the FPSA (62% vs. 39% and 42% vs. 6%, respectively) [82].

DIALIVE is a novel liver dialysis device that incorporates principles of both albumin dialysis and hemadsorption. A recent RCT of 32 ACLF patients found that ACLF resolution was higher (43% vs. 27%) and occurred faster with DIALIVE, compared to standard care, although there was no significant difference in 28-day mortality [83]. DIALIVE-treated patients also had a greater improvement in the kidney sub-score of the CLIF-OF score (along with improvements in the liver, coagulation and brain sub-scores) at Day 10. Although these findings are promising, further studies are warranted.

6 | Liver Transplantation in ACLF: Considerations for Patients With AKI

The definitive management of ACLF is liver transplantation (LT). Studies have shown that preoperative renal function is an independent predictor of survival following LT [13, 84, 85]. Further, the need for KRT is associated with a higher risk of

one-year mortality after LT (HR 2.74, 95% CI:1.37–5.51) [86]. Data also suggests that pre-transplant kidney dysfunction is associated with end-stage kidney disease (ESKD) and a poorer quality of life post-LT [11, 12].

There is evidence, however, that suggests that the aetiology of AKI, rather than the need for pre-transplant KRT or serum creatinine, determines post-LT outcomes. In a retrospective study of 283 patients who underwent LT, Nadim et al. found post-transplant outcomes in those with HRS were similar to those without AKI [87]. However, one- and five-year patient survival was significantly worse in those with ATN. Those with ATN also had a higher incidence of CKD (Stage 4 and above) at five-year follow-up (56% vs. 16%), when compared to those with HRS.

While early LT can reverse HRS-AKI, patients who require KRT for more than 30 days have a higher risk of non-recovery of kidney function post-LT and should be considered for simultaneous liver kidney (SLK) transplantation [29]. SLK may also be considered in those with advanced CKD (eGFR <25 mL/min/1.73m^2) [88]. A key factor in ascertaining eligibility for liver-kidney co-transplantation, therefore, is the determination of reversibility of the kidney dysfunction. This can often be challenging since a kidney biopsy that can provide valuable prognostic information may not be feasible in ACLF patients. There may be a role of biomarkers in this setting; although, at present, there is little research to guide such clinical decisions.

Simultaneous liver kidney transplant (SLK), where both liver and kidney transplants are performed in the same operation, offers several benefits over kidney after liver transplant (KALT). The procedure requires a one-time exposure to anaesthesia and, so, may carry lower risks. It may also have immunological benefits due to exposure to a single set of donor antigens and, therefore, protection from kidney allograft rejection; whereas those planned for KALT may face difficulties in finding a suitable donor due to prior sensitisation from the LT. Indeed, studies have shown higher recipient and allograft survival rates in SLK compared to KALT [89]. On the other hand, KALT avoids unnecessary use of donor kidneys in those who would have gone on to have renal recovery, or in those who would have died irrespective of whether they received a kidney transplant along with the liver. Further, in patients with Grade 3 ACLF where the 28-day survival is less than 10% without a liver transplant, early LT is a priority, and so, KALT may be a better approach [90, 91].

7 | Areas of Uncertainty and Future Directions

It is now recognised that AKI in ACLF is distinct from that occurring in decompensated cirrhosis. Maiwall et al. found that patients with ACLF were significantly less likely to be volume-responsive (21% vs. 34%) and more likely to have structural AKI (32% vs. 18%) than those with decompensated cirrhosis [8]. Progression of AKI (32% vs. 16%) and requirement of kidney replacement therapy (26% vs. 19%) were also higher in ACLF [8]. AKI in the ACLF setting is also associated with poorer short-term survival rates, compared to AKI in decompensated cirrhosis [8, 9]. Likewise, unlike in ACLF patients, AKI in acute liver failure (ALF) is often a consequence of drug toxicity (e.g., acetaminophen-induced ALF) or systemic hemodynamic changes (as seen in ischemic hepatitis or in ALF with superimposed sepsis) [92, 93]. Moreover, medical therapy for HRS-AKI is rarely pursued in ALF and instead, early KRT is advocated due to concerns of worsening cerebral oedema [92]. Despite these differences, management guidelines have been largely extrapolated from studies in patients with decompensated cirrhosis and ALF. Research on AKI specifically in the ACLF setting is lacking, and one of the reasons for this is the lack of a universal definition of ACLF and AKI. Development of standardised definitions can facilitate early diagnosis, improve prognostication and patient management, and encourage collaborative research.

Systemic inflammation is now recognised to be the primary pathophysiological driver of organ failure in ACLF and therefore should be considered as a potential therapeutic target. Extracorporeal techniques such as TPE, CKRT, ECAD and hemadsorption can remove circulating inflammatory mediators and toxins and therefore hold theoretical promise in ACLF. There is a need to explore their role further, moving beyond their current position as predominantly a bridge therapy to LT in eligible patients. The benefits of early therapy in ACLF with terlipressin have been demonstrated by the recent eTerli study. It is conceivable; therefore, that early initiation of extracorporeal therapies may help in limiting or reversing organ damage in ACLF, although there is insufficient evidence at present to recommend their routine use. There is a need for well-designed RCTs to shed light on this question.

There is an urgent need for sensitive tools that can reliably predict AKI in ACLF or identify patients at earlier stages of kidney damage, where the potential for reversibility may be higher. Biomarkers such as NGAL and cystatin C may hold promise in this regard [94, 95]. Biomarkers may also aid in differentiating ATN from HRS-AKI—this distinction is important from a therapeutic and prognostic perspective. There is a need for large multicentre studies to evaluate the utility of biomarkers in the ACLF setting and to define diagnostic thresholds.

Deciding whether to initiate dialysis in a patient with ACLF and severe AKI who is not an eligible candidate for LT can be challenging. Such patients generally have dismal outcomes and therefore, it could be argued that dialysis (or other extracorporeal therapies) may be futile. However, renal recovery may occur in a subset, and assessing the potential for reversibility of AKI is difficult. Consequently, withholding dialysis in LT-ineligible patients poses an ethical dilemma, and a time-limited trial of KRT may be a more reasonable approach. Unfortunately, no prognostic models exist at present to inform such decisions. A shared decision-making approach involving the patient's family, in consultation with a multidisciplinary team of hepatologists, nephrologists and palliative care physicians, is essential to navigate these complex scenarios.

Similarly, identification of patients who are at high risk of mortality and are thus unlikely to benefit from transplantation is also essential to enable efficient allocation of healthcare resources and avoid undue expenditure and patient suffering. In LT-eligible patients with AKI, deciding between LT alone versus SLK is yet another area of uncertainty. Further data from large multicentre studies is needed to provide insights into these areas.

Multimodal risk prediction models incorporating a combination of clinical, laboratory (including biomarkers) and imaging data may be superior to traditional models for guiding decisions on vasopressor therapy, KRT and liver transplantation, and predicting renal recovery or future CKD risk. Application of artificial intelligence (AI) approaches has the potential to improve our understanding of this complex disease, improve upon existing definitions/criteria, and revolutionise patient management.

Author Contributions

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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