Hepatology International
https://doi.org/10.1007/s12072-024-10650-0

GUIDELINES

# APASL clinical practice guidelines on the management of acute kidney injury in acute-on-chronic liver failure

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Received: 30 November 2023 / Accepted: 20 January 2024


## Abstract

Acute-on-chronic liver failure (ACLF) is a syndrome that is characterized by the rapid development of organ failures predisposing these patients to a high risk of short-term early death. The main causes of organ failure in these patients are bacterial infections and systemic inflammation, both of which can be severe. For the majority of these patients, a prompt liver transplant is still the only effective course of treatment. Kidneys are one of the most frequent extrahepatic organs that are affected in patients with ACLF, since acute kidney injury (AKI) is reported in 22.8–34% of patients with ACLF. Approach and management of kidney injury could improve overall outcomes in these patients. Importantly, patients with ACLF more frequently have stage 3 AKI with a low rate of response to the current treatment modalities. The objective of the present position paper is to critically review and analyze the published data on AKI in ACLF, evolve a consensus, and provide recommendations for early diagnosis, pathophysiology, prevention, and management of AKI in patients with ACLF. In the absence of direct evidence, we propose expert opinions for guidance in managing AKI in this very challenging group of patients and focus on areas of future research. This consensus will be of major importance to all hepatologists, liver transplant surgeons, and intensivists across the globe.

**Keywords** AKI · ACLF · Portal hypertension

**Abbreviations**

| | |
|---|---|
| ACLF | Acute-on-chronic liver failure |
| APASL | Asian Pacific Association for the Study of Liver |
| EASL | European Association for the Study of Liver |
| AKI | Acute kidney injury |
| sCr | Serum creatinine |
| KDIGO | Kidney disease improving global outcome |
| ICA | International Club of Ascites |
| UO | Urine output |
| HRS | Hepatorenal syndrome |
| HRS AKI | Hepatorenal syndrome acute kidney injury |
| HRS NAKI | Hepatorenal syndrome non-acute kidney injury |
| CKD | Chronic kidney disease |
| AKD | Acute kidney disease |
| ATN | Acute tubular necrosis |
| CN | Cholemic nephropathy |
| CECT | Contrast-enhanced computed tomography |
| CIN | Contrast-induced nephropathy |
| PICD | Paracentesis-induced circulatory dysfunction |
| ALF | Acute liver failure |
| DC | Decompensated cirrhosis |
| ICU | Intensive care unit |
| LoE | Level of evidence |
| AARC | APASL ACLF Research Consortium |

Extended author information available on the last page of the article

Published online: 05 April 2024

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| SIRS | Systemic inflammatory response syndrome |
| PAMPS | Pathogen-associated molecular patterns |
| DAMPS | Damage-associated molecular patterns |
| UDCA | Ursodeoxycholic acid |
| LT | Liver tansplantation |
| MCP-1 | Monocyte-chemoattractant protein-1 |
| eGFR | Estimated glomerular filtration rate |
| A-HGFR | ACLF high GFR |
| A-LGFR | ACLF low GFR |
| MELD | Model for end stage liver disease |
| NGAL | Neutrophil gelatinase-associated lipocalin |
| IL-18 | Interleukin 18 |
| PRA | Plasma renin activity |
| CysC | Cystatin C |
| KIM-1 | Kidney injury molecule |
| L-FABP | Liver fatty acid-binding protein |
| TIMP2 | Tissue inhibitor of metalloproteinases 2 |
| IGFBP7 | Insulin-like growth factor-binding protein 7 |
| TFF-3 | Trefoil-factor-3 |
| GST | Glutathione-*S*-transferase |
| NAC | *N*-Acetyl cysteine |
| RCT | Randomised control trial |
| SBP | Spontaneous bacterial peritonitis |
| G-CSF | Granulocyte colony-stimulating factor |
| CD 34 | Cluster differentiation |
| SDF | Stromal-derived factor |
| CXCR4 | C–X–C chemokine receptor 4 |
| G CSF | Granulocyte colony-stimulating factor |
| NSBB | Non-selective beta blocker |
| HVPG | Hepatic venous pressure gradient |
| PIRO | Predisposition, insult, response, organ dysfunction |
| IAP | Intra-abdominal pressure |
| RRT | Renal replacement therapy |
| VTI | Inhaled tidal volume |
| IVC | Inferior vena cava |
| ARDS | Acute respiratory distress syndrome |
| MAP | Mean arterial pressure |
| SOFA | Sequential organ failure assessment |
| CRRT | Continuous renal replacement therapy |
| SLED | Sustained low-efficiency dialysis |
| RCA | Regional citrate anticoagulation |
| MDRO | Multidrug-resistant organisms |
| SLKT | Simultaneous liver kidney transplant |
| AD | Acute decompensation |

## Introduction

Acute-on-chronic liver failure (ACLF) is a syndrome which is characterized by the rapid development of organ failures, predisposing these patients to a high risk of short-term early death (33–50%) [1–6]. There are different definitions for ACLF across the world, but the two most widely accepted and validated are the one proposed by the Asian Pacific Association for the Study of Liver (APASL) and the second by the European Association for the Study of Liver (EASL) Chronic Liver Failure (EASL-CLIF) consortium [3, 6]. The Chinese have also proposed a definition, wherein ACLF could be defined as an increase in serum bilirubin above 12 mg/dl and INR above 1.5 in patients with hepatitis B infection. This was shown in a multicentric study conducted across 13 liver centers in China [5]. The presence and severity of systemic inflammation and bacterial infections are the major drivers of organ failure in these patients. Alcohol-related hepatitis, hepatotropic viruses, over-the-counter hepatotoxic drugs, and complementary and alternative medicines have been recognized as the main precipitants of ACLF [1–9]. The data from CANONIC suggest organ support and intensive care unit stay are required for most patients during the natural course of the disease [5]. A timely liver transplant remains the only definitive treatment option for most of these patients [1–5]. The kidneys are one of the most frequent extrahepatic organs that are affected in patients with ACLF, since acute kidney injury (AKI) is reported in 22.8–34% of patients with ACLF. They are also considered an organ of immense utility, and therefore the approach and management of AKI could improve the overall outcomes in these patients [10–12]. Interestingly, patients with ACLF more frequently have stage 3 AKI which in the majority responds poorly to the current modalities [13].

The objective of the present position paper is to provide recommendations for understanding the early diagnosis, pathophysiology, prevention, and management of AKI in patients with ACLF. The document will also address the future development of research in the field. Based on an in-depth review of the relevant literature and active interaction and debates with various experts, we provide a comprehensive document incorporating the consensus statements and the proposed recommendations.

## Methods

The involved panelists (experts) met at New Delhi on 5th March 2023 to develop the consensus. Several groups were formed and waere led by a group leader. The recommendations are graded according to the Oxford Centre for Evidence-Based Medicine system and categorized as ‘weak’ or ‘strong’ based on the consensus agreement between the various experts. When the agreement was more than 80%, it was graded as strong, or else was considered as weak. (Table 1) The final recommendations were based on the results of three rounds of Delphi survey. We endeavor to provide the best available evidence and expert opinion which could enable appropriate clinical decision-making for the

**Table 1** Level of evidence and recommendation

| | |
|---|---|
| Level of evidence | |
| Level 1 | Meta-analysis of randomized controlled trial (RCT) or high-quality RCTs |
| Level 2 | Lesser quality RCTs or prospective comparative studies |
| Level 3 | Case–control studies or retrospective studies |
| Level 4 | Case series without the use of comparison or control group |
| Level 5 | Case reports or expert opinion |
| Recommendations | |
| Strong | Consensus of > 80% |
| Weak | Consensus of < 80% |

physicians involved in the management of patients with ACLF with AKI. The manuscript prepared was circulated to everyone for approval prior to submission.

## Section I: Incidence, definition, spectrum, course, and pathophysiological basis of AKI in ACLF

Acute kidney injury due to liver diseases is associated with significant mortality and a significant healthcare burden in patients with decompensated cirrhosis and ACLF. AKI has been defined either by a rise of more than 0.3 mg/dl (≥ 26.5 µmol/l) serum creatinine within 48 h or around a 50% rise in sCr from the baseline within the last 7 days [14]. For defining AKI, particularly in patients with cirrhosis, the International Club of Ascites (ICA) has incorporated the definition proposed by the kidney disease improving global outcome (KDIGO) [14]. Changes in urine output precede changes in sCr, especially in critically ill patients with cirrhosis. In a retrospective large study by Amathieu et al., incorporation of urine output was shown to increase the sensitivity of AKI diagnosis [15]. Therefore, monitoring urine output facilitates the identification of AKI at an early stage and provides an appropriate window to optimally manage it and prevent its progression. In the setting, critically ill patients showed notably higher mortality if identified based on urine output alone without considering sCr. As per the ICA 2015 consensus, HRS was categorized into HRS-1 and HRS-2 with absolute SCr of > 1.5 mg/dl. Recently, these have been modified to HRS-AKI and HRS-NAKI (non-AKI), respectively, when the patient meets the criterion for AKI irrespective of the absolute SCr value [14] (Fig. 1, Table 2). The main aim of this change is to allow early recognition and treatment of HRS. Commonly, hepatologists and nephrologists manage AKI in three types of medical contexts. These include acute liver failure (ALF), ACLF, and patients with decompensated cirrhosis (DC) [3–5]. One out of five hospitalized patients with cirrhosis develops AKI with a mortality rate of more than 50% [14]. The prevalence of AKI in ACLF is

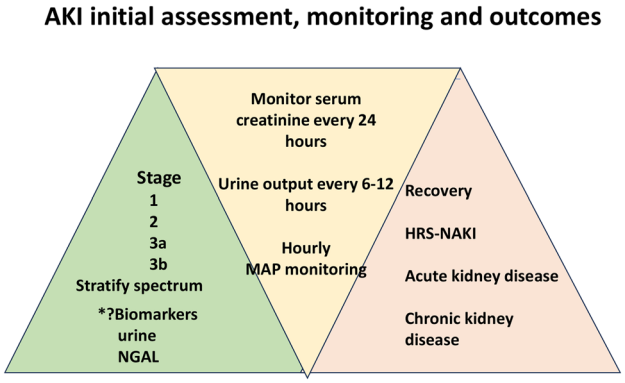



**Fig. 1** The graph depicts the stages of acute kidney injury (AKI) in patients with acute on chronic liver failure (ACLF). The patients need to be monitored with daily serum creatinine with or without urine output and followed for recovery which could be partial or complete or may progress to acute or chronic kidney disease

much higher 22.8%-51% compared to patients with acute decompensation of cirrhosis [11]. AKI associated with ACLF is known to have a higher frequency, more rapid progression, a different spectrum, and higher mortality. In a prospective study performed in patients with ACLF, patients had more structural AKI (32% vs. 18%) and more progression (32% vs. 16%) and requirement of RRT (26% vs. 19%) compared to patients with acute decompensation of cirrhosis. These patients had higher prevalence of tubule epithelial cells and fine and coarse granular casts on microscopic urine analysis. Apart from this, significantly higher markers of systemic inflammation, i.e., leucocyte counts, serum ferritin and higher serum bilirubin, and prevalence of multiorgan failure, were observed in these patients at baseline compared to patients with acute decompensation of cirrhosis. In another study performed in ACLF patients, a higher progression was observed from 13 to 33% of AKI stage 3 which resolved in only one in five patients with vasoconstrictors. Patients with deep jaundice, serum bilirubin more than 23 mg/dl, high MELD more than 35, and AARC grade 3 required dialysis suggesting rapid progression of AKI in patients with ACLF. On histopathology,

**Table 2** Definitions of AKI in ACLF patients and response

| | | |
|---|---|---|
| Acute kidney injury in ACLF patients | | |
| Definition | AKI is defined as rise in more than 0.3 mg/dl (≥ 26.5 µmol/l) serum creatinine (sCr) within 48 h or a 50% rise in sCr from the baseline within the last 7 days or decline in urine output to less than 0.5 ml/kg in 6 h | |
| Staging of AKI | Stage I | Increase in serum creatinine by 1.5- to twofold or increase of more than 0.3 mg/dl in 48 h or a decline in urine output < 0.5 ml/kg/h for 6–12 h |
| | Stage II | Increase in serum creatinine by two to threefold from baseline or a decline in urine output < 0.5 ml/kg/h for ≥ 12 h |
| | Stage III | Increase in serum creatinine > threefold from the baseline or ≥ 4 mg/dl with an acute rise of at least 0.5 mg/dL or requirement of renal replacement therapy<br>**3a** Urine output > 0.3 ml/kg/h<br>**3b** ≤ 0.3 ml/kg/h for ≥ 12 h or anuria for ≥ 24 h |
| Progression | The progression of AKI should be defined as an increase in 1 stage based on either urine output or creatinine criteria | |
| Persistence | Persistence of the same stage | |
| Resolution: The resolution of AKI could be either partial or complete | | |
| Partial | Decline by 1 stage of AKI to a level of serum creatinine > 0.3 mg/dl from the baseline<br>In patients on dialysis, change in AKI stage from 3b to 3a or non-requirement of dialysis for more than 72 h with a spontaneous decline in serum creatinine | |
| Complete | Decline in serum creatinine to 0.3 mg/dl of the baseline value<br>In patients on dialysis, complete recovery could be defined as a sustained recovery of kidney functions with non-requirement of dialysis for > 14 days with the return of serum creatinine to below 1.5 mg/dl and urine output to more than 0.5 ml/kg/h | |

CN was identified in almost two-thirds of patients who died of stage 3 AKI [13]. Further, data from critically ill patients suggests a poor agreement between urine output and sCr. Almost a third of patients are diagnosed with AKI using the urine output criteria with normal sCr. Patients with oliguria lasting more than 12 h (KDIGO stage 2 or 3) have higher ICU mortality [16]. There are no studies specifically evaluating the significance of oliguria in patients with ACLF. Going back to the study by Amathieu et al., using the sCr criteria, 61% of those patients with stage 2–3 AKI based on urine output were actually misclassified as either no AKI or AKI stage 1. Oliguria was identified as an independent predictor of worse outcomes [15]. In another prospective study in critically ill patients with cirrhosis, the urine output preceded changes in sCr. It was also identified as an independent predictor of a worsening AKI course and mortality [17]. Further, urine output is a very important factor in more severe grades of AKI and determines the decision of dialysis initiation. Improvement in urine output is an important sign considered for dialysis discontinuation in the critically ill [18]. Therefore, urine output could be more reliable in staging AKI in patients of ACLF. The challenges in monitoring urine output is the requirement of catheterization, which cannot be routinely recommended. Considering low urine output as a sinister sign determining diagnosis and prognosis in these patients and in general critically ill, a revised AKI staging incorporating urine output is suggested for patients with ACLF. The staging would also help determine recovery in patients on dialysis. We propose a revised staging of AKI incorporating urine output in ACLF patients. We also recommend future studies investigating urine output for diagnosis and staging of AKI in patients with ACLF.

## Incidence and definition of AKI

The incidence of AKI in patients with ACLF is higher compared to those with decompensated cirrhosis. [**LoE4, strong recommendation, consensus 100%**]

AKI in patients with ACLF is defined as either a decline in urine output to less than 0.5 ml/kg in 6 h or a rise of more than 0.3 mg/dl (≥ 26.5 µmol/l) of sCr within 48 h or a 50% rise in sCr from the baseline within the last 7 days. Urine output criteria should be incorporated in the staging of AKI in patients with ACLF. [**LoE4, strong recommendation, consensus 100%**]

Patients with ACLF have a distinct spectrum with a predominance of structural AKI compared to patients with decompensated cirrhosis. **[LoE4, strong recommendation, consensus 97%]**

## Defining progression and recovery of AKI in patients with ACLF

Patients with ACLF have more often a rapid progression of AKI and a lower response to vasoconstrictors compared to patients with decompensated cirrhosis [11]. These patients have a higher prevalence of structural AKI and active sediment on urine microscopy suggesting tubular injury. In critically ill patients with cirrhosis, non-resolution of AKI at day 7 was associated with worse outcomes and higher progression to chronic kidney disease (CKD) [19]. The proximal tubules are the prime victim of injury in inflammation-related AKI. In a prospective study, a higher prevalence of tubule epithelial cells and granular casts (fine and coarse) was observed in patients with ACLF compared to decompensated cirrhosis. The tubule epithelial cells drive tubulointerstitial inflammation and maladaptive repair, leading to renal fibrosis secondary to failure of mitochondrial repair [19]. Patients with non-resolution also showed predominance of macrophage and monocyte infiltration on kidney biopsies. However, these findings have not been studied specifically in patients with ACLF.

Considering the rapidity of AKI development and progression in patients with ACLF, the assessment for progression should be by monitoring urine output (6–12 hourly if patient is catheterized) and sCr every 24 h (Table 2).

## What is the pathophysiological basis of AKI in ACLF?

### The role of systemic inflammation in driving AKI in ACLF patients

The pathophysiological basis of AKI in ACLF can differ when compared to that of AKI in patients with decompensated cirrhosis [11]. A higher degree of systemic inflammation is probably the key driver of the development of organ failures in patients with ACLF including AKI [20–24]. Claria et al. showed a strong association between the severity of systemic inflammation and the development of ACLF syndrome [2]. In a study from AARC, the presence of systemic inflammatory response syndrome (SIRS) was observed in two-thirds of patients with ACLF, and new onset SIRS developed in another one-third of patients by day 7 [20]. In this investigation, the development of SIRS was closely related to the severity of hyperbilirubinemia and the development of renal failure by day 4 which in turn predicted higher 90-day mortality [20]. Patients with ACLF have pre-existing cirrhosis with a structural and functional component of portal hypertension. The former is related to increase in the intrahepatic resistance secondary to architectural distortion due to fibrosis and regenerative nodules, while the latter is related to a vasoactive-induced increase of portal inflow and

intra-hepatic vasoconstriction. The increase of the degree of systemic inflammation drives the enhancement of the functional component of portal hypertension which becomes the predominant component observed in these patients [21]. The increase in the inflammatory cytokines drives increased release of nitric oxide and reactive oxygen species with consequent vasodilatation in the splanchnic and intrahepatic vascular bed and dysregulation of the vasoactive mechanisms on one side and mitochondrial dysfunction and/or damage on the other side. These mechanisms lead to development of all complications including ascites and AKI. There are limited studies on the pathomechanisms of AKI in ACLF. In a multicentric study from AARC, the severity of jaundice, systemic inflammation, and circulatory failure predicted AKI development. Further, patients who developed AKI had higher urea, sCr, potassium, and use of nephrotoxic drugs at enrollment [12]. Gut dysbiosis with bacterial translocation and increased release of pathogen-associated molecular patterns (PAMPs) and of damage-associated molecular patterns (DAMPs) from dying and necrotic hepatocytes cause organ failures. These DAMPs and PAMPs cause activation of the innate and the adaptive immune system. This results in exaggerated systemic inflammation, which further causes organ dysfunction by causing immunopathology and mitochondrial dysfunction [22]. Moreau and colleagues identified a 38-metabolite signature which was related to mitochondrial dysfunction and the severity of ACLF [23]. In another study, Zaccherini et al. evaluated the role of blood amino acids in driving organ failures in patients with ACLF [24]. The amino acids in ACLF fuelled an increase in the protein and nucleotide synthesis, while an enhanced catabolism of ketogenic amino acids was observed in the peripheral organs. They also found a defect in the autophagy secondary to a decrease in the spermidine levels. Systemic inflammation causes activation of the tryptophan degradation through the kynurenine pathway, which produces metabolites causing both multiorgan dysfunction and an immunosuppressive phenotype [25]. In another study by Claria et al., the products of kynurenine pathway were higher in ACLF compared to acute decompensation of cirrhosis. This further increased with the severity of systemic inflammation and ACLF severity and were significantly higher in patients with renal failure [25]. All together, these studies suggest systemic inflammation and circulatory dysfunction in ACLF patients with AKI.

#### The role of bile acids, oxidative stress and renal ischemia

Bile cast nephropathy is further an underrecognized cause of renal dysfunction in ACLF patients. The data on CN is very sparse and only comprises case reports or case series and animal data. This is primarily because kidney biopsy is required for the diagnosis of CN [26–30]. Patients with ACLF are usually very sick and coagulopathic, wherein a kidney biopsy cannot be performed routinely. Fickert and colleagues in an animal model of bile duct ligation elegantly demonstrated a rapidly progressive renal injury mediated by bile acids, which led to tubulointerstitial fibrosis and was abrogated by nor-ursodeoxycholic acid (UDCA) treatment [27]. In a series of 149 patients wherein a kidney biopsy was performed, 17.8% of the patients had evidence of CN. The authors identified serum bilirubin, alkaline phosphatase, urinary bilirubin, and urobilinogen as predictors of CN [31]. C-reactive protein, which is a marker of systemic inflammation, was noted to be higher in patients with CN. In a study performed on post-mortem kidney biopsies, patients with ACLF more frequently had evidence of CN compared to decompensated cirrhosis and it was significantly associated with higher serum bilirubin levels [31]. In another study performed in patients with ACLF, more than two-thirds of patients with ACLF who died with stage 3 AKI had CN. A combination of CN and ATN was observed in a small proportion of patients and only one-third had ATN. The association of CN with bile acids was not evaluated in this study [32]. In the normal physiological state, the bile acids are filtered at the glomerulus, which are absorbed by the apical sodium-dependent transporter and organ solute transporter α/β in the distal part of the loop of Henle [26]. However, in patients with cholestasis, the excess serum bile acids result in compensatory overactivation and saturation of the kidney's ability to excrete the bile acids resulting in CN. In a transgenic animal model of cholemia, the pro-oxidant effects of hydrophobic bile acids on non-hepatic organs, i.e., kidneys, brain, and heart, were also demonstrated [29]. The role of bile acids in causing AKI and dysfunction of other extrahepatic organs needs to be evaluated in patients with ACLF (Fig. 2). The circulatory failure in ACLF patients can be due to hypovolemia, cardiac dysfunction or associated with severe vasodilatory state. There are no studies specifically evaluating the impact of circulatory failure on renal microcirculation in ACLF patients. With renal ischemia, there is an impaired delivery of oxygen and blood supply, particularly to the outer medulla. There is an imbalance between the demand and supply which affects the kidneys either focally or diffusely. This causes tubular epithelial cell and endothelial injury, causing apoptosis, and when severe results in acute tubular necrosis [33]. The impact of circulatory failure in causing both the development and persistence of AKI has been shown in different studies [12, 17, 34]. In the context of sepsis, specific phenotypes have been recognized. Complex pathogenetic mechanisms such as complement activation, inflammation, impairment of microcirculation, defective autophagy, and metabolic reprogramming have been implicated in the development of sepsis-associated AKI. How septic shock drives AKI in ACLF including the lactate kinetics in the context of sepsis-induced circulatory failure is worth being investigated.

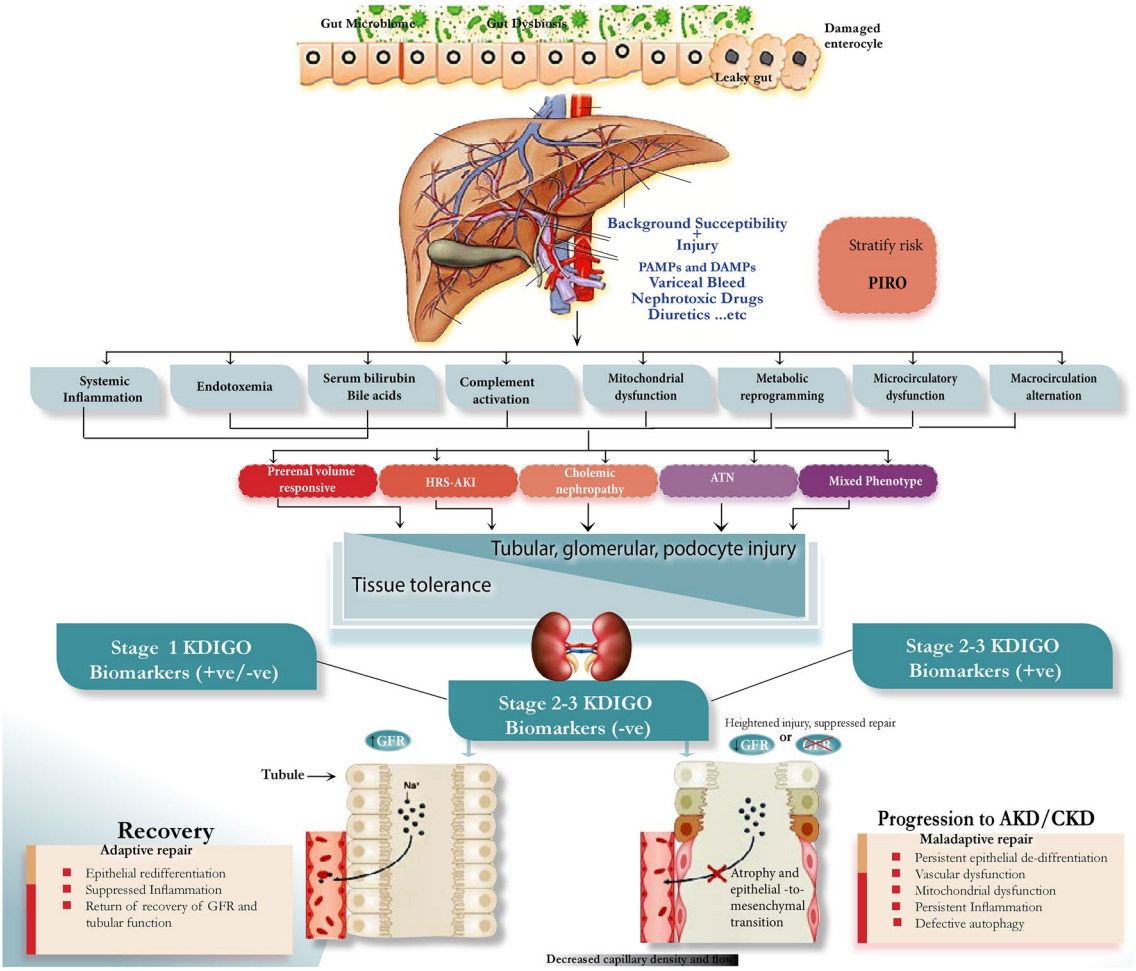



**Fig. 2** Patients with acute on chronic liver failure have gut dysbiosis and leaky gut causing endotoxemia, release of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide, and of damage-associated molecular patterns (DAMPs) from dying and injured hepatocytes which causes immune dysregulation. Superimposed on the background susceptibility, patients develop several insults to the kidneys, which can predispose to the development of acute kidney injury that is the most frequent extrahepatic organ involved in these patients. The risk of AKI can be stratified by the PIRO model (predisposition, injury, response, and organ failure). Several other factors, such as metabolic reprogramming, toxicity due to bile acids, severity of systemic inflammation, mitochondrial dysfunction, and micro or microcirculatory dysfunction, determine the phenotype and severity of AKI. A complex interplay between background susceptibility, precipitating insults, and host response determine outcomes. Patients can be risk stratified by AKI stages using the serum creatinine or urine output and the role of biomarkers in each stage may determine the type and course of AKI. The role of biomarkers even though exciting cannot be routinely recommended in ACLF patients with AKI. The final outcomes could involve repair and recovery to normal glomerular filtration rate, which is more likely in lower stages of AKI and biomarker-negative cases, while the risk of progression to acute or chronic kidney disease is more likely in patients with more severe AKI and biomarker-positive patients and those with structural kidney damage. Patients with maladaptive repair have persistent inflammation in the tubulointerstitial compartment, failed repair, and had progression to renal fibrosis

## Gut dysbiosis and AKI

The liver and gastrointestinal tract communicate through the bile duct and portal vein. Gut dysbiosis is the change in the structure or composition of gut microbes which define a specific phenotype. Gut dysbiosis, especially the bacterial translocation across the gut epithelial barrier, may not only cause progression of the disease but also drive kidney injury. Various studies have shown a production of excessive uremic toxins (indoxyl sulfate, p-cresyl sulfate, and trimethylamine-N-oxide) due to gut dysbiosis [35]. In a study comparing 98 patients with liver cirrhosis, compared to 83 healthy controls, 36.1% of novel genes were identified. These genes could then be categorized into 66 clusters, of which 28 were enriched in patients, most of which were of buccal origin [36]. In animal models of ischemia/reperfusion injury, an increase of Enterobacteriaceae, decrease of lactobacilli, and Ruminococcaceae were observed which were associated with higher intestinal inflammation, disruption of the gut epithelial barrier causing leaky gut, and

decreased levels of short-chain fatty acids [37]. The role of the gut–liver–kidney axis remains to be explored in patients with ACLF.

#### Statements

The presence of endotoxemia, severity of systemic inflammation, high serum levels of bilirubin, and circulatory dysfunction are key determinants in the pathophysiological basis of AKI in patients with ACLF. [**LoE4, strong recommendation, consensus 100%**]

The plausible effects of bile acids, oxidative stress, and renal ischemia contribute to the pathophysiology of AKI in patients with ACLF. [**LoE5, strong recommendation, consensus 100%**]

### Does AKI transition to CKD in patients with ACLF?

Traditionally, kidney diseases are categorized into acute and chronic at a 3-month cutoff. The mortality risk in AKI is associated with severity of liver disease (higher grade of ACLF) and more severe renal dysfunction (higher stage of AKI) [13]. AKI can evolve to acute kidney disease (AKD) or to CKD if the renal injury persists for more than 7 or 90 days, respectively. The outcomes of AKD include resolution, recurrence, progression to CKD, or death [38]. In a large study of 6250 patients with cirrhosis, Patidar and colleagues showed that almost one in three hospitalized patients with cirrhosis and AKI developed AKD, which was associated with higher mortality and risk of de-novo CKD [39]. In the context of outpatients of cirrhosis, in a study of 272 patients, Tonon et al. showed that almost one-third developed AKD, of which 50% recovered from the first episode and 14% had progression to CKD [40]. In a prospective study, AKI leads to future AKI [41] and almost one-third of the patients with AKI developed CKD. The number, severity, duration of AKI, and the severity of liver disease are key determinants of the development of CKD, and kidney biopsy showed predominance of tubule–interstitial inflammation [42]. Similarly, Bassegoda et al. demonstrated that the transition of AKI to CKD was associated with an increased 3-month hospital readmission rate, bacterial infections, refractory ascites, and a trend toward a higher need for liver transplantation (LT) [43]. The risk of CKD development could be predicted by cystatin C. However, unfortunately, none of these studies included patients with ACLF. There are several mechanisms implicated in the development of CKD. Patients who have defective repair mechanisms and continued inflammation develop CKD and associated cardiovascular complications. The repair is usually considered complete if the renal perfusion and glomerular and tubular function returns back to normal. On the contrary, a maladaptive repair in the tubulointerstitial compartment leads to the development of renal fibrosis. The key mechanisms leading to a maladaptive repair include injury to the renal tubule epithelial cells, endothelial injury, infiltration by the monocytes and macrophages, mitochondrial dysfunction, and defective autophagy [44]. In the context of critically ill patients with inflammation or infection-driven AKI, the incidence of progression to CKD was observed in almost 50%. The presence and persistence of renal tubule epithelial cells and/or granular casts at enrollment and day 7 were independent predictors of CKD development [17, 19]. Patients who failed to recover at day 7 had significant elevation in the tubular and endothelial injury markers and higher levels of monocyte-chemoattractant protein-1 (MCP-1) and defective function of the mitochondrial genes in the renal tubule epithelial cells [19]. Persistent AKI or worsening of AKI are more likely in patients with higher stages of AKI (AKI stage 2 or 3); thus, they are more likely to progress to CKD. Despite RRT, death rates are high in these patients without liver transplant. Many patients of ACLF with severe AKI may not survive 3 months to meet the (arbitrary) 3 months transition time window from AKI to CKD. A retrospective study analyzed the impact of ACLF before LT on short-term kidney function. As per EASL CLIF definition of ACLF, 356 non-ACLF patients, 32 ACLF patients with eGFR $\geq$ 30 mL/min/1.73 $m^2$ (A-HGFR), and 28 ACLF patients with eGFR < 30 mL/min/1.73 $m^2$ (A-LGFR) were studied. The slopes of eGFR before the 3-month post-LT increased in the A-LGFR group (+ 7.26 mL/min/1.73 $m^2$/month), remained stable in the A-HGFR group (+ 1.05 mL/min/1.73 $m^2$/month), and declined in the non-ACLF group (-7.61 mL/min/1.73 $m.^2$/month). The A-LGFR group had increased risk of developing composite kidney outcomes (eGFR < 15 mL/min/1.73 m or need for dialysis) in adjusted analysis, (hazard ratio [HR] = 3.61, 95% confidence interval [CI] 1.35–9.70) compared with the non-ACLF group. However, this significance disappeared on further adjusting for eGFR at 3-month post-LT (HR = 1.91, 95% CI 0.70–5.23). The renal dysfunction in the A-LGFR group stabilized after partial recovery by 3-month post-LT (eGFR reset point) [45].

#### Statement 1a

There is limited data on the transition of AKI to AKD and CKD in ACLF patients. **[LoE5, strong recommendation, consensus 100%].**

### Statement 1b

ACLF patients with AKI stage 2 or 3 are more likely to have non-resolution of AKI, development of AKD, and the transition to CKD and hence require close monitoring. **[LoE5, strong recommendation, consensus 100%].**

## Which are the risk factors of AKI in patients with ACLF?

The common risk factors of AKI in ACLF can be liver related or kidney related, and other factors including use of nephrotoxic drugs.

### Drugs and the mechanism of kidney injury

The common antimicrobials implicated in the development of AKI include aminoglycoside antibiotics, polymyxin group, vancomycin, amphotericin B, and fluoroquinolones. The mechanisms include proximal or distal tubulopathy with electrolyte wasting, acute tubular damage, or crystal deposition or acute interstitial nephritis. Diuretics may perpetuate AKI by causing renal hypoperfusion. Also, in the presence of hypovolemia or decreased GFR, diuretics can precipitate AKI [46]. The angiotensin-converting enzyme inhibitors cause systemic vasodilatation and vasodilatation in the renal vascular bad at the efferent arterioles. The commonly used drugs and the implicated mechanisms are summarized in Table 3. Hypovolemia and sodium depletion can cause AKI with the use of these drugs [47, 48]. Radiographic contrast agents are implicated in contrast-induced nephropathy. The mechanisms of contrast-induced nephropathy include renal medullary hypoxia, oxidative stress, and epigenetic regulation secondary to immune/inflammatory damage and apoptosis. Risk stratification and prevention is the key, as the drugs combating oxidative stress have limited role. There are no studies assessing the incidence of contrast-induced nephropathy in patients with ACLF. Guevara and colleagues studied the impact of cirrhosis on the development of contrast-induced nephropathy. In 31 patients of cirrhosis, 20 with ascites and 5 with renal failure, detailed assessment of renal function with glomerular filtration rate using iothalamate I-125 clearance and renal plasma flow using iodohippurate I-131 clearance before and 48 h after the administration of contrast media was performed. The administration of contrast media was not associated with renal function impairment even in those with renal failure. However, an increase in urinary prostaglandin E2 and *N*-acetyl-beta-D-glucosaminidase was observed. They further investigated a prospective cohort of 60 patients with cirrhosis and renal failure and did not find any patient developing contrast-induced nephropathy [49]. In a recent large multicentric prospective cohort study which aimed to evaluate the incidence and predisposing factors of AKI in patients with cirrhosis undergoing contrast-enhanced computed tomography (CECT) including 444 inpatients, three cohorts of patients were analyzed. Cohort 1 included 148 patients with cirrhosis which was compared to cohort 3, which included 163 patients without cirrhosis undergoing CECT. This cohort was compared to a cohort of 133 patients with cirrhosis (cohort 2) who were unexposed to iodinated contrast media. A detailed assessment of kidney function parameters was performed at T0, 48–72 h (T1) and 5 and 7 days after CECT/enrollment. Urinary neutrophil gelatinase-associated lipocalin (U-NGAL) was measured in 50 consecutive patients from cohort 1 and 50 from cohort 2. The AKI incidence was not significantly increased in patients with cirrhosis undergoing CECT (4.8%, 1.5%, 2.5% in cohorts 1, 2, and 3, respectively, $p = \text{ns}$) and the presence of concomitant infections was the only independent predictive factor of CI-AKI (OR 22.18, 95% CI 2.87–171.22, $p = 0.003$). No significant modifications of NGAL were also detected [50]. Patients with ACLF, however, are a distinct group and risk of CIN should be considered as the data is limited.

### Liver-related risk factors

The pathophysiologic mechanisms detail the liver-related risk factors. In a large cohort study including 1032 patients with ACLF, higher MELD score, presence of ascites, sepsis, and acute variceal bleed were identified as risk factors of AKI development [51]. Raised intraabdominal pressures causing intraabdominal hypertension could also contribute to AKI development in ACLF patients. AKI in the context of paracentesis-induced circulatory dysfunction (PICD) is also more often seen in patients with ACLF. Patients with ACLF develop PICD even after a modest volume of paracentesis (i.e., less than 5 l). In a single-center randomized controlled trial, PICD developed in 70% in patients of ACLF undergoing modest-volume paracentesis which was reduced to 30% with the use of intravenous 20% albumin. AKI developed in 62% vs. 30% in patients who received versus who did not receive albumin, respectively [52].

### Kidney-related risk factors

The presence of background CKD and concomitant use of nephrotoxic agents are implicated in AKI development, which can vary from mild injury to severe renal damage [46]. Apart from these risk factors, the development of AKI in turn leads to new AKI development and therefore should be recorded for all patients. The severity, duration, and type of AKI determine outcomes including the development of CKD. This is possibly because with each AKI episode, there is a loss of functional nephrons which can lead to decrease in the renal reserve [53]. In a large cohort of outpatients with

**Table 3** Common drugs, the mechanism of renal injury, and management

| Drug group | Type/mechanism of injury | Studies in liver disease | Management |
|---|---|---|---|
| Renin–angiotensin system inhibitors [43, 49, 50]<br>ACE inhibitors<br>ARB inhibitors | Inhibits efferent arteriolar vasoconstriction, thereby causing decreased blood flow and intraglomerular hydrostatic pressure | Conflicting results in cirrhosis, avoided in decompensated cirrhosis | (1) Discontinuation of ACEI/ARB<br>(2) Correction of hypovolemia |
| Non-selective beta blockers [51]<br>(e.g., propranolol, carvedilol) | Reduces mean arterial pressure (MAP), thereby reducing renal perfusion | Study done in patients of alcoholic hepatitis showed higher incidence of AKI with NSBB | (1) Discontinuation of NSBB<br>(2) Correction of hypovolemia<br>(3) Maintaining MAP > 65 mmHg |
| NSAIDS [52, 53]<br>(e.g., ibuprofen, naproxen, diclofenac, aceclofenac) | (1) Inhibition of vasodilation-causing prostaglandins such as PGE2, thereby decreasing renal perfusion<br>(2) Acute interstital nephritis due to immunological reaction after NSAID ingestion | COX-2 inhibitors may be safer than non-selective NSAIDs | (1) Discontinuation of NSAID<br>(2) Correction of hypovolemia<br>(3) Short course of steroids may be needed in case of AIN due to NSAIDs |
| Diuretics [37]<br>(e.g., furosemide, toresemide, spironolactone, eplerenone) | Reduced renal perfusion due to depletion of effective blood volume | Overzealous use leads to risk of hypovolemia | (1) Discontinuation of diuretics<br>(2) Correction of hypovolemia |
| Antibiotics | | | |
| Aminoglycosides [54, 55]<br>(gentamicin, neomycin, amikacin) | Aminoglycosides causes tubular damage through necrosis of proximal tubular epithelial cells, predominantly in the proximal tubule | Study showed aminoglycoside nephrotoxicity is frequent in advanced cirrhosis | Adjust dose for eGFR. N-acetylcysteine demonstrates promising protective effects on patients using aminoglycosides |
| Glycopeptide [56, 57]<br>(vancomycin, teicoplanin, telavancin) | There is immune-mediated acute interstitial nephritis, tubular necrosis due to mitochondrial inhibition, and oxidative damage | Used to treat Gram-positive infection in cirrhosis, leading to rise in creatinine in hypovolemic patients and those with previous history of AKI | Adjust dose for underlying eGFR<br>Therapeutic drug monitoring is required |
| Colistin/polymyxins [58, 59] | Nephrotoxicity is via an increase in tubular epithelial cell membrane permeability | Among 249 patients treated with colistin, rates of AKI were 12% and 29% at 48 h and 7 days, respectively | Adjust dose for underlying eGFR<br>Avoid prolonged use<br>Use alternative agents |
| Amphotericin B [60] | Amphotericin B binds to sterols in cell membranes, cholesterol causing tubular injury | No large-volume studies | Use lipid or liposomal forms IV isotonic, crystalloid hydration |

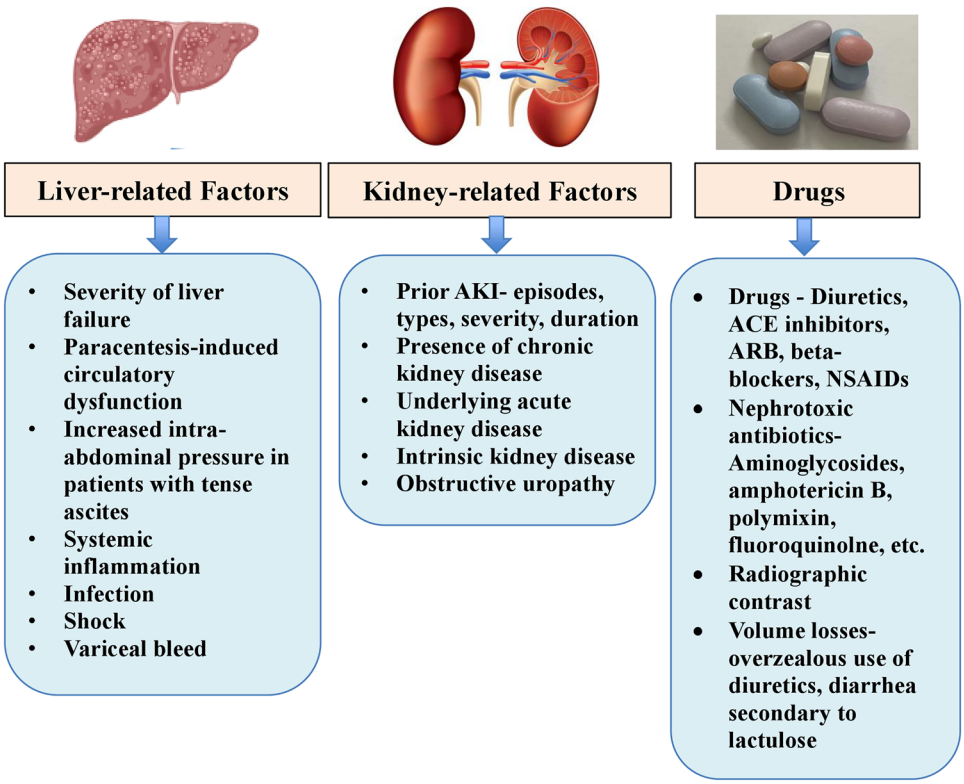



**Fig. 3** The risk factors for acute kidney injury can be stratified as liver related, kidney related, and others. Nephrotoxic antibiotics should be cautiously used and drugs like angiotensin-converting enzyme inhibitors or receptor blockers should be permanently discontinued. Diuretics should be carefully monitored for and higher doses may be fraught with lowering of mean arterial pressure and cause AKI development

stable decompensated cirrhosis, cystatin C, higher bilirubin, and prior AKI were identified as independent predictors of new development of AKI [41]. Risk factors are given in Table 3 [54–65] and Fig. 3.

### Statement

The risk factors of AKI in ACLF can be stratified as liver and kidney related and as extraneous factors particularly the use of nephrotoxic drugs. **[LoE4, strong recommendation, consensus 97%].**

### Recommendation

A detailed clinical history and assessment of risk factors should be performed in all patients with ACLF and AKI. Record and stratification of risk factors as liver or kidney related and as extraneous factors particularly drugs should be considered. **[LoE4, strong recommendation, consensus 97%].**

## Section II: Biomarkers of AKI in ACLF

Early recognition of AKI and accurate measurement of renal function in cirrhosis are crucial in the management of these patients. Persistence of AKI in patients with ACLF is associated with a higher in-hospital mortality [34]. Though urine output and sCr can detect AKI, these lack sensitivity and specificity. Further, they cannot determine the phenotype of AKI, and whether AKI is due to functional or structural cause. In patients with ACLF, intense systemic and splanchnic vasodilatation secondary to intense systemic inflammation very often causes capillary leak. The decline in urine output may occur due to third spacing and serum creatinine may result in underestimation of renal functions in such patients. At the same time, diuretic use may lead to an overestimation of renal function. The most frequently used laboratory value to measure GFR is sCr, because it is readily available, inexpensive, and accurate. However, sCr has many factors that influence its value, such as race, age, gender, and muscle mass. Patients with cirrhosis including ACLF are malnourished, cachectic, and sarcopenic, leading to a deficiency in protein intake which is associated with muscle wasting and leads to underestimation of renal function. These patient-specific factors could be reasons for a lower sCr, leading to an overestimation of GFR and renal function. Another factor leading to inaccuracy in creatinine correlating with GFR is that hyperbilirubinemia affects Jaffe's kinetic assay that measures sCr and leads to an inaccurately low measurement. Despite this, sCr remains the primary measurement of renal function in cirrhosis because it is cost-effective, can be measured easily, and can be repeated, and the use of novel biomarkers is still in development (Table 4).

*Cystatin C* is a low-molecular-weight protein that is produced by all nucleated cells. It is filtered by the glomerulus

**Table 4** Biomarkers in ACLF

| Biomarker | Investigators | Methodology | Conclusion | Comment on ACLF |
|---|---|---|---|---|
| Cystatin C | Jha et al. 2022 | Forty-seven patients were included in the study. Serum cystatin C was analyzed with the development of AKI and the outcome | Serum cystatin C is a better predictor for AKI development compared to serum creatinine | Cystatin C may be used as an early marker for new-onset AKI in hospitalized patients with ACLF |
| Cystatin C | Wan et al. 2013 | Fifty-six consecutive patients with hepatitis B virus-related ACLF were included | Serum CysC provides early prediction of renal dysfunction in ACLF patients with a normal serum Cr level | CysC level was an independent risk factor for AKI development The cutoff value of serum CysC for prediction of AKI in ACLF patients was 1.21 mg/L |
| FABP, IL 18, NGAL, cystatin C | Saha et al. 2022 | 91 patients with EASL ACLF were included | Biomarkers are not effective at discriminating between ACLF patients having AKI (ACLF-AKI) and ACLF patients without AKI (ACLF no-AKI) | IL-18, which is a measure of inflammation, is able to predict mortality in ACLF patients and Cystatin C is able to discriminate between ACLF-AKI and non-liver AKI |
| Cystatin C | Markwardt et al. 2017 | CysC and NGAL in 429 patients hospitalized for acute decompensation of cirrhosis in the EASL CANONIC | Plasma cystatin C, but not NGAL predicted HRS and renal dysfunction | Baseline CysC is a biomarker of renal dysfunction, HRS, and ACLF |
| NGAL, cystatin C | Lu et al. 2019 | Studied NGAL and CysC in predicting the 90-day mortality in HBV-ACLF | NGAL, but not CysC, significantly improved the MELD score in predicting the prognosis of HBV-ACLF | The serum NGAL superior to CysC in predicting the prognosis of HBV-ACLF |
| Cystatin C | Maiwall et al. 2018 | Five hundred and thirty-one cirrhotic without ongoing AKI were followed for development/resolution of AKI | Cystatin C as an independent predictor of new AKI<br>MELD-cystatin score predicted the development of AKI and mortality | Only cirrhosis patients were included |
| NGAL | Ariza et al. 2016 | Analyzed urine and plasma NGAL levels in 716 patients hospitalized for complications of cirrhosis, 148 with ACLF | Urine NGAL improved significantly the accuracy of MELD in predicting prognosis The *LCN2* gene was markedly upregulated in the liver of patients with ACLF | NGAL is a biomarker of ACLF and prognosis and correlates with liver failure and systemic inflammation |
| NGAL, CysC, L-FABP, IL-18 | Jiang et al. 2018 | 280 patients with hepatitis B virus (HBV)-related ACLF (HBV-ACLF) and 132 patients with HBV-related decompensated cirrhosis were enrolled | AKI in ACLF patients is more likely associated with structural kidney injury, and is more progressive, with a poorer response to terlipressin treatment | NGAL, CysC, L-FABP, IL-18 were significantly elevated in patients with HBV-ACLF and AKI |
| KIM 1, NGAL, cystatin C | Lei et al. 2018 | This study involved 150 patients divided into AKI and non-AKI, and healthy individuals | Urinary KIM-1 and NGAL concentrations and serum Cys C levels were significantly higher in patients with AKI secondary to decompensated cirrhosis | KIM 1 not assessed in ACLF |
| FABP | Kulkarni et al. 2021 | Patients with alcohol-ACLF and age-matched healthy controls. FABPs were analyzed by enzyme-linked immunosorbent assay method | A-FABP, L-FABP, AARC score, and serum protein predicted mortality in alcohol ACLF | Adipocte-FABP is highly sensitive at predicting mortality and outcome in alcohol ACLF |
| Osteopontin, TIMP 1 | Levitsky et al. 2019 | Serum samples pre-LT and 4–12 weeks post-LT ($n = 117$) were analyzed for kidney injury proteins | In patients with elevated pre-LT serum levels of OPN and TIMP-1, recovery of renal function correlated with decreases in the level of both proteins | Not assessed in ACLF patients |

and mainly reabsorbed by the proximal tubule. Despite the limitations, cystatin C is not affected by age, muscle mass, malignancy, or inflammation. The assay, unlike sCr, is not affected by high levels of serum bilirubin and combination equations of Cr and cystatin C are superior to sCr. Cystatin C is an independent predictor of AKI and outcomes, including mortality. In a cohort of 55 patients with hepatitis B virus-related ACLF who had normal sCr level, CysC level was an independent risk factor for AKI development (odds ratio = 1.8; 95% CI 1.4–2.3, $p = 0.021$). The cutoff value of serum CysC for prediction of AKI in ACLF patients was 1.21 mg/L [66]. In another single-center study that included all patients with cirrhosis listed for LT, on multivariable competing risk analysis, CysC ≥ 1.5 mg/L, sarcopenia and albumin were independent predictors of mortality. The estimated glomerular filtration rate by CKD–EPI–CysC–creatinine < 60 mL/min/1.73 m at wait list was an independent predictor of the need for RRT in the first month post-LT. [67] In another small cohort study including 47 patients, in which AKI developed in 34%, the best cutoff for baseline CysC was 1.47 mg/L with a sensitivity of 0.94 and specificity of 0.68 (area under the curve [AUC] = 0.853) and was better than that of creatinine (AUC = 0.699). CysC was an independent positive predictor of AKI [68–72].

*Urine neutrophil gelatinase-associated lipocalin (NGAL)* is a small protein made by the kidney, lung, stomach, and colon. Previous studies have shown that NGAL was upregulated in the prerenal AKI and ATN setting and that increased urinary NGAL could be detected within 2 h of initial renal injury. Multiple studies have evaluated the efficacy and utility of urinary NGAL in cirrhosis patients with AKI. Studies had found that urinary NGAL was superior to cystatin C in the diagnosis of AKI or ATN. Barreto et al. studied 132 cirrhotic patients hospitalized with infections and found that among patients with persistent AKI, HRS-AKI could be accurately predicted with urinary NGAL values lower than 86 µg/g creatinine in 88% of patients [73]. Kim et al. studied urinary NGAL and CysC in 328 decompensated cirrhosis patients (41 patients with AKI). The authors found that urinary NGAL is a predictor of AKI and outcomes (including mortality) [74]. Recently, Huelin et al. studied urinary NGAL and IL-18 of 320 cirrhosis patients with AKI. Urinary NGAL was elevated in AKI progression during hospitalization and was predictive of AKI progression in conjunction with MELD score [75]. Currently, there are no definitive diagnostic thresholds for differentiation between these types of AKI. Ariza and colleagues analyzed urine and plasma NGAL levels in 716 patients hospitalized for cirrhosis with complications, of which 148 had ACLF [76]. In another study of 55 patients with acute decompensation of cirrhosis, 34 with ACLF, a panel of 12 urinary biomarkers was assessed. NGAL had the best accuracy for the ATN diagnosis, along with urine IL-18, albumin, trefoil-factor-3 (TFF-3), and glutathione-*S*-transferase-π (GST-π) [77]. In critically ill patients with cirrhosis, urine NGAL predicted the need for RRT, non-response to terlipressin, non-resolution of AKI at day7, and the development of de-novo CKD [19]. In another study of 162 patients with decompensated cirrhosis and AKI, urine NGAL could determine ATN and non-response to terlipressin in HRS-AKI and was an independent predictor of in-hospital mortality [78].

*IL-18* is a proinflammatory cytokine expressed in the proximal tubule. It is released in urine when the cells are damaged in AKI. Urinary IL-18 is elevated in patients with AKI, especially from ischemic injury, but urinary IL-18 is not elevated in conditions such as urinary tract infections, nephrotoxic injury, and CKD. Tsai et al. in 2013 evaluated the clinical outcomes of 168 cirrhotic patients with AKI and severe sepsis. They found that urinary IL-18 was significantly higher in patients with ATN than patients with functional AKI, proposing a cutoff of 708.5 pg/mg creatinine to differentiate between the two groups. Urinary IL-18 was found to be a stronger predictor of ATN than serum IL-18 and they found that elevated urinary IL-18 was associated with higher hospital mortality [79].

*KIM-1* is elevated in AKI from ischemic injury to the proximal tubule. Belcher et al. evaluated KIM-1 in patients with AKI with other etiologies (PRA, ATN, and HRS) and found the highest elevation in ATN with some overlap with HRS. Other studies found that in patients with cirrhosis, elevations in urinary KIM-1 levels were increased mainly in ATN compared to other AKI presentations and could serve as a prognostic indicator [80].

*L-FABP* is a small protein found in the proximal tubular epithelium and binds to free fatty acids when reabsorbed in the proximal tubule. L-FABP may be elevated in sepsis and specific etiologies of CKD (diabetic nephropathy or glomerulonephritis). Eguchi et al. studied L-FABP in 242 chronic liver disease patients (chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma) [81]. The authors found that serum L-FABP increased in liver cirrhosis compared to chronic hepatitis and is higher in the presence of hepatocellular carcinoma. L-FABP correlates with kidney function markers, especially BUN, creatinine, and GFR. This study shows the potential for L-FABP in chronic liver disease and other complications, including AKI. In a pilot study of 25 patients with alcohol-related ACLF, adipocyte fatty acid-binding protein (A-FABP) levels were associated with the development of new organ failures, including renal failure [82]. Pro-C6, a biomarker of extracellular matrix, was shown to positively correlate with markers of AKI including urinary neutrophil gelatinase-associated lipocalcin (NGAL). Elevated levels were also associated with extrahepatic organ failures and higher short-term mortality.

Two new biomarkers being studied for potential benefits are insulin-like growth factor-binding protein-7 and

tissue matrix metalloproteinase inhibitor-2. They are only approved for evaluating AKI in patients with intensive care unit (ICU) and need further evaluation. There is not enough evidence to note potential utility. Very few studies have analyzed the role of urinary biomarkers as predictors of response to therapy. Although urinary NGAL at day 3 predicted the need for RRT, it was not associated with a response to terlipressin. Urinary biomarkers of cell cycle arrest, TIMP-2 and IGFBP7, also did not predict response to terlipressin in patients with HRS [83]. Novel biomarkers can differentiate both the degree of renal dysfunction and possible etiology, but the data are not substantial enough to currently recommend utility. Additionally, these tests are not readily available and are expensive methods to evaluate renal function [84–86]. Almost all these molecules provide retrospective information, i.e., they indicate that damage has already occurred in the renal parenchyma. This "retrospective" aspect of biomarkers might be useful to detect the development of CKD in patients with ACLF in the pre- or post-transplant setting. Early detection of an ongoing damage with the use of a "prospective" biomarker would be very useful to assess the efficacy of preventive therapeutic approach. One could speculate that a biomarker that monitors metabolism of renal epithelial cells before these cells die would be very useful.

### Can biomarkers be used for timely diagnosis of AKI in ACLF?

CysC and other biomarkers are of interest in predicting AKI in patients with decompensated cirrhosis. Because data for patients with ACLF are lacking, studies are needed on the use of biomarkers in these patients. **[LoE 5, strong recommendation, consensus 97%].**

### Can biomarkers delineate the spectrum of AKI in ACLF (HRS-AKI from ATN)?

Biomarkers, especially urine NGAL, are of use in differentiating ATN from HRS-AKI in patients with decompensated cirrhosis. Because of limited data on NGAL in patients with ACLF, studies need to be conducted. [**LoE 5, weak recommendation, consensus 97%].**

### Can biomarkers guide the prediction of the course of AKI in ACLF and the timely initiation of terlipressin?

In the patient with ACLF, the progression of AKI is associated with increased mortality. There is some evidence that biomarkers, in particular urine NGAL, predict the short-term progression of AKI in patients with decompensated cirrhosis. Because data on biomarkers are lacking in patients with ACLF, studies should be conducted to assess the predictive value of biomarkers in these patients.

#### Statement

There is limited data using biomarkers to decide on initiating terlipressin therapy for HRS-AKI. **[LoE 5, strong recommendation, consensus 97%].**

### Can biomarkers *aid* in deciding the need for dialysis in patients with ACLF?

There are no studies that address the use of biomarkers for deciding the need for dialysis. Biomarkers alone, outside standard criteria for RRT initiation, cannot be used for deciding the need for dialysis in patients with ACLF. [**LoE 5, weak recommendation**, **consensus 97%].**

### Can biomarkers predict renal recovery in ACLF patients?

Some biomarkers (e.g., urine NGAL) are of interest in predicting renal recovery in patients with decompensated cirrhosis. Because data for patients with ACLF are lacking, studies need to be conducted on biomarkers for renal recovery prediction in these patients. [**LoE 5, weak recommendation**, **consensus 97%].**

### Can biomarkers guide the risk of CKD development pre- and post-transplant in ACLF patients?

Biomarkers (e.g., urine NGAL) may prove to be useful in guiding the risk of development of CKD in patients with cirrhosis pre- and post-transplant. Because data for patients with ACLF are lacking, studies need to be conducted on biomarkers for CKD development in these patients. [**LoE 5, weak recommendation, consensus 97%**].

## Section III: Prevention of AKI in ACLF

### Predictive models for AKI in ACLF

Predictive models are required for risk stratification in patients with ACLF. In a large study including patients with 397 decompensated and hospitalized patients with cirrhosis, a predictive model comprising white blood cell count, high sCr, and international normalized ratio was developed and validated for prediction of AKI [87]. However, this was developed from a single-centre and the mean MELD of the included patients was 17. The PIRO model was developed from the large multinational database and showed good predictive ability for AKI in patients with ACLF, however,

has not been validated outside the Asia–Pacific region [12] (Fig. 4).

## Role of antioxidants in AKI prevention

Multiple studies have explored the role of *N*-acetyl cysteine (NAC), antioxidants, and other agents in the prevention of AKI; however, most of these were post hoc analysis. In a small retrospective study of hepatitis B-related ACLF, 42 patients who received *N*-acetylcysteine were compared to 48 patients in the control group [88]. In an open-label RCT, investigating the omega 6 vs. omega 3 infusions compared to standard medical treatment in patients with ACLF, a significant reduction in the incidence of sepsis by day -28 was observed in the omega 6 and omega 3 fatty acid group compared to standard medical treatment, i.e., 40% (22.65–59.4) in omega 6, 13.34% (0.03–39.72) in omega 3 vs. 60% (40.6–77.34) ($p < 0.001$). On post hoc analysis, a concomitant and significant reduction in sCr was also observed. However, the impact on AKI development was not studied [89]. In RCT including patients with severe alcohol-related hepatitis, 48 patients on antioxidants (combination of beta-carotene, vitamin C and E, selenium, methionine, NAC) were compared to 53 patients randomized to corticosteroids, and a lower proportion of patients developed renal failure and sepsis in the antioxidant group (23% vs. 11%) [90]. NAC combined with enteral nutrition compared to enteral nutrition did not show benefits in AKI development [91]. In the randomized controlled trial comparing a combination of glucocorticoids and NAC versus glucocorticoids, a significant reduction in the incidence of the syndrome (HRS) [25%vs. 12%, 0.41; 0.17–0.98; $p = 0.02$] and mortality due to HRS [22% vs. 9%; 2.79; 95% CI 1.08–7.42; $p = 0.02$] was observed with NAC [92] Three RCTs on alcohol-related hepatitis evaluating the role of pentoxifylline did not show the benefits in AKI prevention [93–95]. NAC is the recommended drug of choice for acetaminophen-induced ALF. It is the drug of choice for ALF due to any cause and has been documented to improve transplant-free survival (TFS) in patients with grade 1–2 encephalopathy, but not advanced stages [96, 97]. In a retrospective analysis from China, NAC infusion was shown to improve intrahepatic cholestasis and coagulation dysfunction with significant reduction in serum bilirubin in patients with HBV-related ACLF [98]. The improvement in serum creatinine, however, was not observed in this study.

## Intravenous albumin for AKI prevention

In a recent position paper involving 33 experts from 19 different countries, several recommendations on the use of intravenous albumin in patients with decompensated cirrhosis were proposed. However, no recommendations

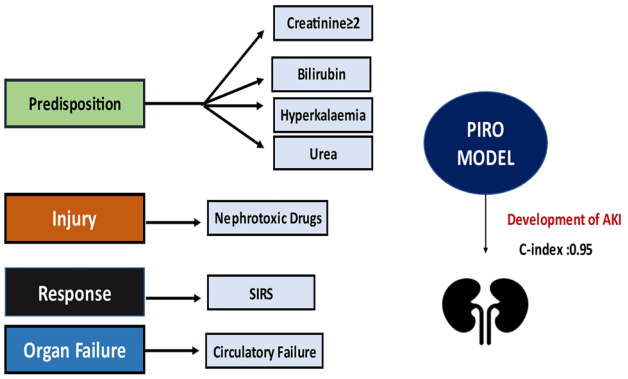



**Fig. 4** The components of the PIRO score, the only score developed specifically for predicting AKI risk in patients with ACLF, comprises four components. Predisposition—serum bilirubin, urea, creatinine and potassium, injury secondary to nephrotoxic drugs, response as components of systemic inflammatory response syndrome, and organ failure secondary to microcirculatory dysfunction or shock

were proposed specifically for patients with ACLF. For patients with acute decompensation of cirrhosis, the consensus felt lack of benefits with short-term use of human albumin. [99] In RCT including 80 patients with ACLF, undergoing therapeutic paracentesis of < 5 l, PICD was more frequent in the non-albumin group compared to patients who received albumin (70% vs. 30%; $p = 0.001$), including a higher incidence of hepatic encephalopathy (50% versus 27.5%; $p = 0.04$), hyponatremia (67.5% versus 22.5%; $p < 0.001$), AKI (62.5% versus 30%; $p = 0.001$), and 28-day mortality (62.5% versus 27.5%; $p = 0.003$). [52] In patients with spontaneous bacterial peritonitis (SBP), Sort et al. randomized 126 patients into two groups: the first received 20% albumin at a dose of 1.5 g/kg at diagnosis and 1 g/kg on day 3 in infusion + cefotaxime; and the second received cefotaxime alone. The incidence of AKI and in-hospital and 90-day mortality was higher in the group without albumin (33% vs 10%, $p = 0.002$), (29% vs 10%, $p = 0.01$) and (41% vs 22%, $p = 0.03$), respectively [100]. Based on this trial, the guidelines recommend the combined use of albumin and antibiotics in patients with SBP, particularly in high-risk groups (bilirubin > 4 mg/dl, blood urea nitrogen > 30 mg/dl and/or creatinine > 1 mg/dl) [101]. However, the data on non-SBP infections failed to show a survival benefit with intravenous albumin. In the INFECIR-2 study, 118 patients with hospitalized cirrhosis with non-SBP infections were randomized to albumin and antibiotics versus antibiotics alone. A significantly higher proportion of patients in the study group had resolution of ACLF (82.3% vs 33.3%; $p = 0.03$) and lower incidence of the development of nosocomial infections (6.6% vs 24.6%; $p = 0.007$) with no difference in mortality. In the pilot Preciosa study, the impact of high dose of albumin was evaluated for 12 weeks in decompensated patients, i.e., 1.5 g/kg weekly versus 1 g/

kg every 2 weeks. The higher doses of albumin were found to be associated with normalization of serum albumin levels, left ventricular circulatory stability, and reduced levels of inflammatory cytokines, but not with any significant changes in portal pressure [102].

### Use of G-CSF in ACLF

G-CSF is a glycoprotein that stimulates the bone marrow to produce and release neutrophils and stem cells (CD34+) into the bloodstream. In response to hepatic injury, the expression of CXC chemokine, stromal-derived factor-1 (SDF-1), and its receptor CXCR4+ increases in the regenerating liver leading to recruitment of HSCs to the peripheral blood. Mookerjee et al. have shown that neutrophil dysfunction leads to the development of sepsis and further to the development of HRS and hepatic encephalopathy in patients with alcohol-related hepatitis superimposed on cirrhosis [103]. There are five randomized controlled trials evaluating the impact of G-CSF therapy on outcomes of ACLF with mixed results. The data from Asian studies have been contrary to the data from European studies. Possibly, the selection of patients and the differences in definitions in these trials could explain the heterogeneity of the results [104–113]. However, in animal models of ACLF, the combination of TAK-242 and G-CSF was shown to inhibit inflammation, promoted hepatic regeneration, and prevented mortality [107]. Based on the data, currently G-CSF cannot be recommended for prevention of AKI in ACLF.

### Use of non-selective beta-blockers (NSBB)

The impact of non-selective beta-blockers on AKI outcomes have been evaluated in two studies. In a retrospective cohort study including data from the CANONIC study, 164 patients on NSBB were compared to 185 patients not on NSBBs. A lower 28-day mortality was observed in patients on NSBB (24.4% vs. 34.1%; $p=0.04$) including a reduction in the ACLF grade and a significantly lower worsening [114]. In an RCT enrolling patients with ACLF with small/no varices and HVPG above 12 mm of Hg, use of NSBBs was associated with lower 28-day mortality (24.3% vs. 10.6%; $p=0.04$) and lower AKI development (13.6%vs. 35.7%; $p=0.003$). However, the effects were not sustained at 60 and 90 days [115]. Although the studies show some benefit, all experts believed on cautious use of NSBB in patients with ACLF.

### Use of prophylactic antibiotics

In an RCT investigating the effect of norfloxacin on the prevention of bacterial infections in 143 ACLF patients, a lower prevalence was observed with norfloxacin compared to placebo at day 28 (18.1% vs. 33.8%; $p=0.03$) and day 90 (46% vs. 62%; $p=0.02$). Almost one-third of the patients developed multidrug-resistant organisms and a higher proportion of patients developed candiduria in the norfloxacin group (25% vs. 2.63%) compared to the placebo group, respectively. [116] Therefore, currently, limited data exist on routine use of norfloxacin in patients with ACLF for prevention of AKI.

### Can the PIRO model be used for risk-stratifying AKI in patients with ACLF?

The components of PIRO include high serum bilirubin, urea, potassium, and creatinine along with the use of nephrotoxic drugs, systemic inflammation, and circulatory failure. The model had good sensitivity and specificity and was developed from the multinational database. The model could be used for risk stratification of AKI, but needs further validation. The role of bile acids could also be explored in this context. [**LoE4, weak recommendation, consensus 90%**].

#### Recommendations

Intravenous albumin is recommended for preventing the development of PICD after modest-volume therapeutic paracentesis. [**LoE2, strong recommendation, consensus 97%).**

Albumin should also be used for preventing the development of renal dysfunction in the context of SBP. The dose of albumin needs to be individualized based on the volume status. [**LoE4, strong recommendation, consensus 91%**].

There is no data to suggest the role of G-CSF, pentoxifylline, and/or antioxidants in the prevention of AKI development in ACLF patients. [**LoE4, strong recommendation, consensus 97%**].

Studies show some benefits of beta-blockers in ACLF patients. However, beta-blockers cannot be recommended for the prevention of AKI in ACLF patients. ACLF patients already on NSBBs should be stopped or dose reduced, as NSBB can decrease the renal blood flow and perfusion and increase the risk of developing AKI. [**LoE4, weak recommendation, consensus 91%**].

The use of prophylactic norfloxacin decreased the incidence of bacterial infections; however, the benefits in the context of AKI have not been studied. Use of prophylactic antibiotics cannot be recommended for the prevention of AKI in patients with ACLF. [**LoE5, weak recommendation, consensus 84.8%**].

## Section IV: Management of AKI in ACLF

### Section IVA: Fluid management in AKI in ACLF

We suggest targeting the goal of maintaining an appropriate perfusion pressure, which is the difference of the mean

arterial pressure (MAP) and central venous pressure. There are four phases of fluid management, rescue, optimization, stabilization, and de-escalation [117–122]. Overzealous fluid administration results in impairment of organ function, particularly of the encapsulated organs. There is organ edema which causes architectural distortion of the vascular bed, reduced capillary flow, and lymphatic return causing decreased renal blood flow and glomerular filtration rate [121, 122]. Measurement of intraabdominal pressures may be used as a guide to target an appropriate renal perfusion pressure by preventing increased renal venous pressure. The kidneys are most vulnerable to even small increases in IAP. An arterial Doppler of the renal arteries could guide detecting compromised renal microvascular blood flow. Hypervolemia can also cause gut edema along with bacterial translocation, cytokine release, and oxidative stress and reduction in cardiac output. In a randomized controlled trial evaluating a restrictive fluid strategy targeting negative or neutral fluid balance compared to usual care showed reduced incidence of RRT (RR 0.42, 95% CI 0.16–0.91; $p=0.043$) with the restrictive strategy [123]. Similar results were observed in a large multicentric randomized controlled trial, the FACTT trial, which included patients with acute lung injury; a conservative fluid strategy was associated with improved outcomes. The strategy was associated with a decrease in the duration of mechanical ventilation without increasing the need for RRT [124].

The initial assessment of the ACLF patient with AKI should be based on the detailed history of all the risk factors (as detailed above) and a clinical examination**.** Specific clinical signs to be carefully assessed include recording the MAP, pulse, and orthostatic changes in blood pressure. Other signs include a decline in urine output, mentation, capillary refill time and skin turgor or dryness, and skin perfusion (mottling/cold extremities). The initial laboratory assessment should include (if feasible and/or the patient is in the intensive care unit) recording the arterial lactate, pH, base excess, bicarbonate, central venous oxygenation, and/or mixed venous $PCO_2$.

### Should intravenous albumin be initiated for the management of stage 1 AKI in ACLF?

The recommendations for the management of ACLF patients should be different from those of patients with decompensated cirrhosis. This is because the AKI in ACLF is different from decompensated cirrhosis and 48 h of waiting may be detrimental. Systemic inflammatory response plays a more important role apart from the hemodynamic dysfunction in the pathogenesis of organ failure in ACLF. Therefore, initiation of intravenous albumin for volume expansion should be initiated at stage 1 in these patients, unlike patients with decompensated cirrhosis [22, 50]. Albumin in these patients would correct the effective hypovolemia through its oncotic properties and ameliorate systemic inflammation through its immunomodulatory and endothelial stabilization function [102]. However, there are no studies evaluating the impact of intravenous albumin in stage 1 AKI in patients with ACLF. (Fig. 5).

**Statement** Initiation of volume expansion with albumin in stage 1 of AKI may improve resolution and prevent progression in patients with ACLF [**LoE4**]. However, the evidence for initiation of albumin in stage 1 AKI in ACLF is limited.

Initiation of volume expansion with albumin at stage 1 AKI in patients with ACLF is recommended. Close monitoring should be done to prevent volume overload. [**LoE4, strong recommendation, consensus 100%**].

### Should 5% albumin be used for fluid resuscitation in patients with ACLF and AKI with shock?

The large randomized controlled trial, the FRISC protocol, comparing 5% albumin versus normal saline for fluid resuscitation in critically ill patients with cirrhosis and sepsis-induced hypotension [125]; showed the superiority of 5% albumin over normal saline for fluid resuscitation. In this RCT, 250 mL 5% albumin given as bolus was superior to normal saline in causing reversal of shock and improvement in tachycardia, arterial lactate, and urine output. This was also associated with survival benefit at 7 days. Similarly, the SAFE study was a multicentric trial comparing 4% albumin versus normal saline in critically ill patients requiring volume resuscitation, not necessarily cirrhosis [126]. In the subgroup of patients with sepsis, the superiority of 4% albumin was observed. However, both these trials were not performed in ACLF patients (Figs. 6, 7). In the ALPS trial, 20% albumin was superior to PlasmaLyte in improving the MAP and lactate clearance and was also associated with a prolonged time to RRT [127]. The protocol violations were significantly more in the albumin group. The use of 20% albumin vs. PlasmaLyte was an independent determinant of adverse events along with the presence of pneumonia, higher SOFA scores, and lower serum bicarbonate. PlasmaLyte was a safe fluid in sicker patients and caused fewer pulmonary events. The choice between a balanced crystalloid and normal saline has also been investigated in multiple studies. Animal and human experiments have established the association of 0.9% saline with the development of hyperchloremic acidosis when administered in large volumes. Hyperchloremia is associated with renal vasoconstriction, impairs the renal artery flow velocity, and decreases the glomerular filtration rate by causing cortical tissue perfusion compared to balanced crystalloids [128–130]. In a large cohort study performed on critically ill patients with cirrhosis, hyperchloremia was identified as an independent predictor of AKI non-resolution

at day 7 [17]. In a multicenter, cluster-randomized double-crossover feasibility study conducted in New Zealand, 2300 participants, who needed crystalloids for volume resuscitation without established renal failure requiring RRT, were included. These patients were randomly assigned to 0.9% saline or PlasmaLyte [131]. The incidence of AKI and the need for RRT were not significantly different between the two groups. Another cluster-randomized, multiple-crossover trial including 15,802 adults compared normal saline (0.9% sodium chloride) and balanced crystalloids (lactated Ringer's solution or PlasmaLyte). The patients in the balanced crystalloid group compared to the normal saline group had a reduction in the composite outcome, which included reduced incidence of major adverse kidney events (14.3% vs. 15.4%; $p=0.04$) and in-hospital mortality at 30 days (10.3% vs. 11.1%; $p=0.06$), and, a reducede incidence of RRT (2.5% and 2.9%; $p=0.08$). [132] In another double-blind RCT, comparing PlasmaLyte with saline recruiting 5037 patients, the risk of death or AKI was not different between the two groups [133]. The data therefore suggest the safety of balanced crystalloids in reducing adverse kidney events compared to normal saline, particularly when the volume of fluid required is more. Based on this indirect evidence, we recommend a careful volume assessment of ACLF patients with AKI. Further, a combination of crystalloids with albumin may be preferred in ACLF patients with AKI requiring large amounts of fluids. This is based on a study showing lesser mortality in sepsis patients receiving crystalloids alone versus those receiving early combination of crystalloids with albumin within 24 h (12.5% vs 16.4%, $p=0.003$) [134]. Balanced crystalloids can be used for resuscitation in patients with ACLF and AKI when the volume of fluid required is more.

**Statement 2a** 4% or 5% albumin should be preferred for volume expansion in patients with ACLF, AKI, and shock and should preferably be given within the first 3 h of hospitalization. [**LoE2**].

**Statement 2b** Balanced crystalloids can be used in addition to 4–5% albumin for resuscitation in patients with ACLF and AKI when a greater volume of fluid is required [**LoE5**].

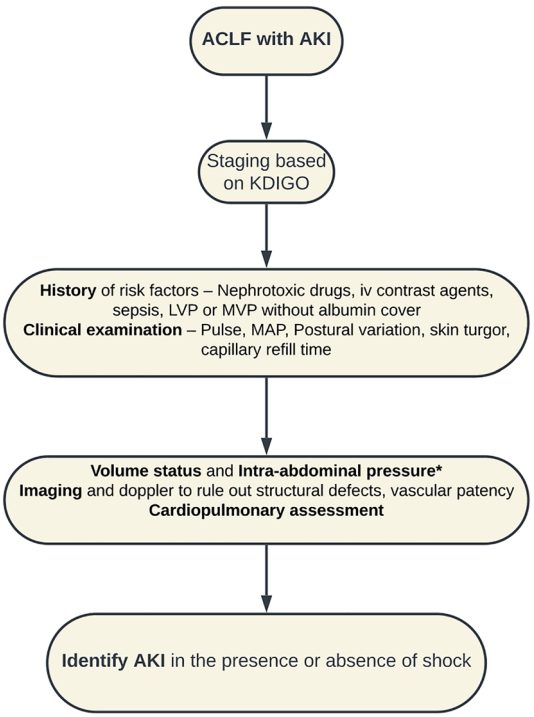



**Fig. 5** Assessment of severity and cause of acute kidney injury, volume, and hemodynamic status for guidance on choice and volume of fluid. The initial assessment should begin with detailed history and physical examination to determine the severity of AKI, cause of AKI, volume, and hemodynamic and cardiopulmonary status of the patient. *KDIGO* kidney disease improving global outcome criteria, L*V*P large-volume paracentesis, *MVP* modest-volume paracentesis (less than 5 l), *MAP* mean arterial pressure

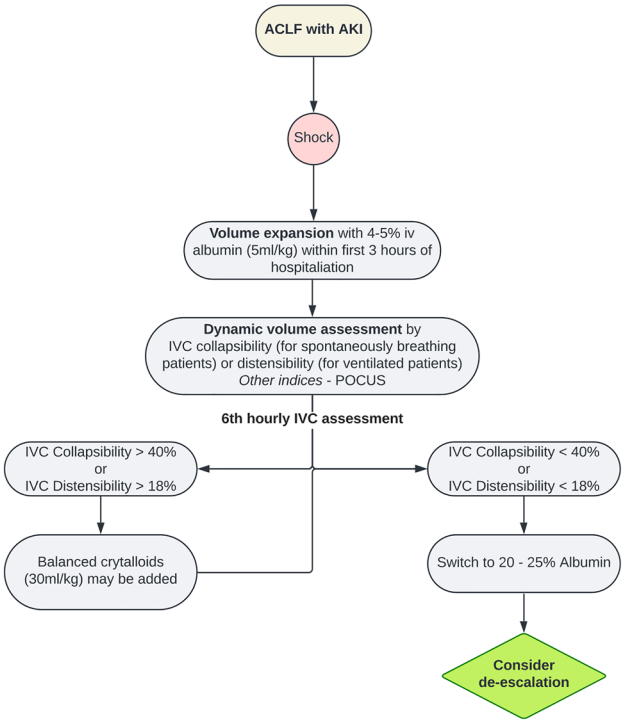



**Fig. 6** Fluid management in ACLF patient with acute kidney injury (AKI) with shock. Patients who are found to be hemodynamically unstable should receive volume resuscitation with 4-5% albumin at a dose of 5 ml/kg, within the first 3 h of presentation, with simultaneous admission to a critical care unit. Dynamic volume assessment should be performed by utilizing IVC collapsibility/distensibility and point of care ultrasound. Those who are found to be volume depleted (IVC collapsibility > 40%) with shock may be additionally given balanced crystalloids. Those with no further scope of fluid may be switched to 20–25% albumin with a daily assessment for de-escalation

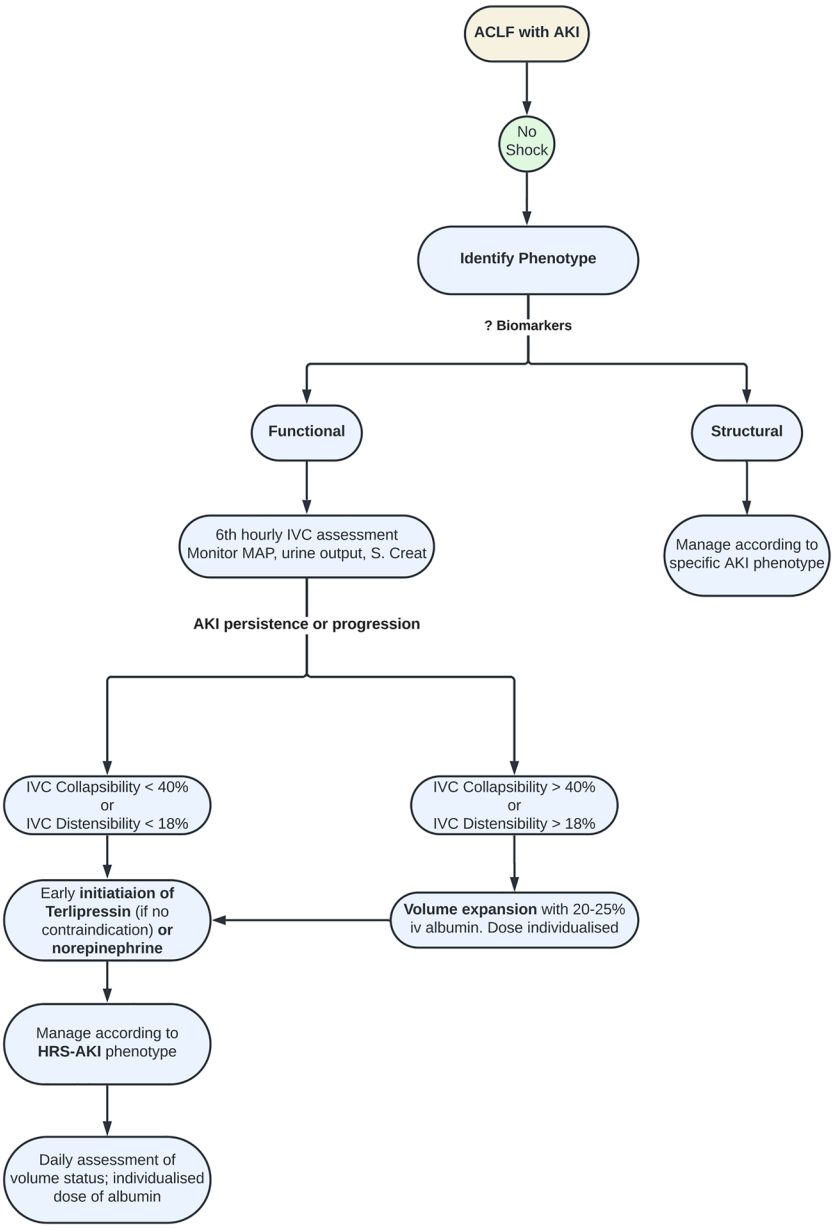



**Fig. 7** Fluid management in ACLF patient with acute kidney injury (AKI) without shock. For patients who are hemodynamically stable and found to have stage 1 AKI may be volume repleted with 20-25% albumin with de-escalation upon response. Those with stage 2 or 3 AKI as per KDIGO should be evaluated for identification of the phenotype of AKI. Biomarkers may be used to differentiate one from the other. For those with HRS-AKI, who are volume depleted, resuscitation with 20-25% albumin is recommended, with early initiation of terlipressin after appropriate volume expansion, starting at a dose of 2 mg/24 h is recommended. *ACLF* acute-on-chronic liver failure, *AKI* acute kidney injury, *LVP* large-volume paracentesis, *MVP* modest-volume paracentesis, *MAP* Mean arterial pressure, *IVC* inferior vena cava, *POCUS* point of care ultrasound, *U Na* urine sodium, *ATN* acute tubular necrosis

**Statement 2c** 20–25% albumin should be used for volume expansion for patients with ACLF and AKI in the absence of shock [**LoE2**].

**Recommendation 2a** In patients with hypovolemia, AKI, and shock, 4–5% albumin should be used for fluid resuscitation compared to crystalloids or 20–25% albumin. [**LoE2, weak recommendation, consensus 91%**].

**Recommendation 2b** Balanced crystalloids can be added to 4–5% albumin for fluid resuscitation when larger volumes of fluid are required. [**LoE5, strong recommendation, consensus 97%**].

**Recommendation 2c** 20–25% albumin should be used for volume expansion for patients with ACLF and AKI in the absence of shock. [**LoE2, strong recommendation, consensus 100%**].

### What should be the appropriate dose of albumin for the management of AKI in patients with ACLF?

Patients with ACLF with AKI usually have severe systemic inflammation, capillary leak, and third spacing predisposing them to risk of pulmonary complications with overzealous use of albumin [22, 23]. It is suggested to use dynamic indices over static indices for guiding the dose of albumin to be administered in patients with ACLF and AKI [121, 122, 135].

The static indices include right atrial, central venous, and pulmonary artery occlusion pressure. Other measures include the assessment of right ventricular end-diastolic volume and global-end diastolic volume by transesophageal or transthoracic echocardiography. Fluid responsiveness is defined by an increase in cardiac output after the fluid challenge (250–500 ml of crystalloid or 3 ml/kg colloid) [128]. The stroke volume is calculated by measuring the aortic velocity time integral. Changes in the stroke volume can be perceived with interventions, i.e., before and after a fluid bolus, or passive leg raising test [128–130]. An increase in the stroke volume by 12–15% indicates volume responsiveness. If the patients are mechanically ventilated, a respirophasic variation of the VTI by 12% is considered a sign of preload dependence. Passive leg-raising test can be used for spontaneously breathing patients. In mechanically ventilated patients, stroke volume variation, pulse pressure variation, end-expiratory occlusion test, measurement of diameter, and collapsibility of superior and inferior vena cava could be used. The measurement of IVC can be used for both fluid responsiveness and fluid tolerance. The variation in diameter and collapsibility are reversed in patients on positive pressure ventilation. Therefore, during inspiration, there is increase in the distensibility of the IVC during inspiration rather than collapse. The collapsibility index is calculated as (IVC maximum–IVC minimum)/IVC maximum and is seen to vary from 12 to 42%. The measurement of extravascular lung water and pulmonary vascular permeability index using the transpulmonary thermodilution technique could be additional guides to the volume management in mechanically ventilated patients. Apart from this, the use of point-of-care ultrasound using the B-protocol and count of the B lines could guide the volume of fluid that should be administered to these patients. The presence of diffuse B-lines suggests either interstitial–alveolar syndrome or cardiogenic pulmonary edema. The lung ultrasound also has an advantage of dynamic assessment, and it can be used for assessing response to the treatment modalities [136–143]. In patients with ARDS, specific findings include reduced pleural motion and abnormalities, and subpleural consolidations. The measurement of intraabdominal pressures could also guide an appropriate renal perfusion pressure by preventing the increase in the renal venous pressure by hypervolemia. However, limited data supports a routine measurement of intraabdominal pressure in patients with ACLF. Based on the availability and expertise and whether the patient is admitted to the intensive care unit, physicians should manage these patients (Fig. 7).

**Statement** The dose of albumin for the management of AKI in ACLF patients should be individualized and guided by dynamic indices, preferably by IVC measurement and lung ultrasound [**LoE4**].

**Recommendation** Patients with ACLF and AKI should receive intravenous volume expansion with intravenous albumin, the dose of which should be individualized and guided by the dynamic indices of fluid responsiveness. [**LoE4, strong recommendation, consensus 94%**].

### Should intraabdominal pressure measurement be routinely performed for ACLF patients with AKI and tense ascites?

**Statement** Measurement of intraabdominal pressures may improve outcomes of AKI in patients with ACLF with tense ascites. However, this currently cannot be recommended in routine clinical practice given lack of data. [**LoE5, weak recommendation, consensus 78%**].

**Recommendation** Measurement of intraabdominal pressures may be performed in patients with ACLF with tense ascites for improving AKI outcomes [**LoE5, weak recommendation, consensus 78%**].

### Does a cardiopulmonary assessment help in patients with signs of hypervolemia or comorbid diseases to decide the administration of albumin in patients with ACLF and AKI?

The ATTIRE trial which enrolled hospitalized patients with decompensated cirrhosis aimed to study the targeted albumin administration compared to the standard of care. The albumin infusions were given targeting serum albumin above 3 gm/dl and a composite outcome of infections, development of renal dysfunction, and mortality were assessed. The study did not show the superiority of targeted albumin and additionally demonstrated a higher incidence of pulmonary events [144]. Similarly, in the ALPS trial, rapid administration of 20% albumin led to a higher incidence of pulmonary complications [127]. A recent investigation by Premkumar et al. on the presence of cirrhotic cardiomyopathy could predict HRS non-response and survival in patients with cirrhosis. Higher levels of CysC and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) also predicted non-response. Adverse events were observed in almost a third of these patients. Although cardiac function and lung ultrasound scores correlated with mortality, an association with the adverse events was not assessed [145]. The CONFIRM trial showed a higher incidence of pulmonary complications in the combination of albumin and terlipressin arm compared to albumin alone [146]. All these patients had AKI-HRS and therefore, met the EASL criteria for ACLF. Together, these studies suggest a predisposition of patients of ACLF with AKI to develop cardiopulmonary events suggesting a need for cardiopulmonary assessment wherever possible. This should be routinely performed in the intensive

care unit, and also in patients on the medical floors wherever feasible. (Table 5, Fig. 8)

**Statement** A cardiopulmonary assessment is helpful in patients with signs of hypervolemia or comorbid diseases to decide the administration of albumin in patients with ACLF and AKI. [**LoE4, strong recommendation, consensus 97%**].

**Recommendation** A cardiopulmonary assessment may decrease the incidence of adverse events to 20% albumin and should be incorporated during the management of ACLF patients with AKI, especially in patients admitted to the intensive care unit. [**LoE5, strong recommendation, consensus 97%**].

## Section IVB: Vasoconstrictors in the management of AKI in ACLF

In ACLF patients with HRS-AKI, the superiority of terlipressin administered as a continuous infusion over norepinephrine has been demonstrated. In the RCT by Arora et al., the response at day 4 [26.7% vs. 11.7%; $p=0.03$], day 7 [40% vs. 20%; $p=0.01$], and day 14 [40% vs. 16.7%; $p=0.004$] with continuous infusion of terlipressin, respectively, was superior to that with norepinephrine. Terlipressin also conferred a significant survival benefit over norepinephrine. Based on this study, terlipressin administered as a continuous infusion should be the first choice for the management of HRS-AKI in patients with ACLF [147].

### Statement

Continuous infusion of terlipressin has been shown superior to norepinephrine in reversing HRS-AKI in patients with ACLF**. [LoE 2, strong recommendation, consensus 94%].**

### Recommendation

Terlipressin administered as a continuous infusion is the vasoconstrictor of choice for the management of HRS-AKI in ACLF patients in the absence of contraindications. **[LoE2, strong recommendation, consensus 94%].**

The time of initiation of terlipressin should be determined based on a dynamic assessment of AKI with persistence/progression after appropriate volume expansion of the patient with intravenous albumin [34]. Vasoconstrictors, particularly terlipressin and noradrenaline are effective in HRS-AKI [146]. However, their efficacy in HRS-AKI for ACLF patients has been suboptimal. Inflammatory markers have an important role in the pathogenesis of AKI in ACLF. This profound change of the pathophysiological background may affect the efficacy of the treatment of HRS by vasoconstrictors plus albumin in patients with ACLF. It is well known that systemic inflammation can reduce organ perfusion due to vasodilation and impaired left ventricular function [11, 12, 34]. It can also impair renal and extrarenal organ function through direct deleterious effects of inflammatory mediators on essential tissue and cell homeostatic mechanisms, including local microcirculation, mitochondrial function, and apoptosis. Progression of AKI is rapid in ACLF patients [11]. These patients therefore have a higher incidence and progression of AKI, as well as more frequent structural kidney damage, which is also associated with worse outcomes [147–150]. Baseline sCr or early improvements in sCr are accurate predictors of treatment response and patient survival. Diagnosis of HRS-AKI in ACLF currently requires 48 h of volume repletion with albumin and diuretic withdrawal. Waiting for 48 h before initiating treatment with vasoconstrictors can be associated with worsening of AKI stage and ACLF stage, and thereby suboptimal treatment response. Piano et al. reported a very high mortality rate in ACLF HRS-AKI stage III both in responders and non-responders to vasoconstrictors [151]. In a randomized controlled trial, eTERLI study, Singh and colleagues demonstrated early initiation of terlipressin as a better strategy. They compared early initiation (ET) of terlipressin at 12 h to waiting for 48 h (ST) in reversing HRS-AKI in patients with ACLF. In the early group, AKI response at day 7 was observed in 24/35 (68.6%) patients compared to 11/35(31.4%) in the ST arm [$p=0.03$]. Full AKI response at day 3 was 31.4% in the ET vs. 11.4% in the ST arm [$p$-0.04]. More patients died within 28 days in the ST than the ET arm [65.7%vs.40%, $p$-0.031] [152].

### Statement

Waiting for 48 h after initial volume expansion is associated with a lower reversal and higher need for dialysis; therefore, an early initiation of vasoconstrictors for ACLF patients with HRS-AKI should be considered. **[LoE2, strong recommendation, consensus 90%].**

### Recommendation

Dynamic monitoring with sCr every 24 h or every 12 h with urine output (in catheterized patients) for initiation of vasoconstrictors at AKI persistence/progression after initial appropriate volume expansion with albumin for management of HRS-AKI in ACLF patients is recommended. **[LoE2, strong recommendation, consensus 88%].**

Boyer and colleagues demonstrated that patients who achieved HRS reversal had a significant rise in the mean arterial pressure (MAP); however, on the contrary, the rise in MAP did not predict the reversal of HRS-AKI [153]. In the RCT by Nazar and colleagues, patients with an increase

**Table 5** Studies of albumin and vasoconstrictors in HRS-AKI

| Study | Methodology | Renal dysfunction | Conclusion |
|---|---|---|---|
| Solanki et al. 2003 | Randomly assigned 24 consecutive patients with HRS to treatment with terlipressin 1 mg i.v. at 12-h intervals (group A; $n=12$) or placebo at 12-h intervals (group B; $n=12$) | After terlipressin treatment, urine output improved, creatinine clearance improved | Terlipressin significantly improved renal functions and systemic hemodynamics |
| Alessandria et al. 2007 | Patients were randomly assigned to be treated with noradrenalin (0.1–0.7 microg/kg/min) and albumin (10 patients) or with terlipressin (1–2 mg/4 h) and albumin (12 patients) | Reversal of HRS was observed in 7 of the 10 patients (70%) treated with noradrenalin and in 10 of the 12 patients (83%) treated with terlipressin | Study suggest that noradrenalin is as effective and safe as terlipressin in patients with HRS |
| Sanyal et al. 2008 | Fifty-six subjects were randomized to each arm. Subjects with type 1 HRS were randomized to terlipressin (1 mg intravenously every 6 h) or placebo plus albumin in both groups | Terlipressin was superior to placebo for HRS reversal (34% vs 13%, $p=0.008$), defined by decrease in SCr level | Terlipressin is an effective treatment to improve renal function in HRS type 1 |
| Sharma et al. 2008 | Forty patients with HRS were randomized to noradrenaline 0.5–3.0 mg/h and albumin (group A, $n=20$) or terlipressin 0.5–2 mg, 6 hourly and albumin (group B, $n=20$) | Patients in both groups had a significant ($p<0.05$) decrease in serum creatinine from baseline (group A day 4, $2.4\pm1.2$ mg/dL and group B day 4, $2.5\pm1.5$ mg/dL | Noradrenaline may be an effective and safe alternative to terlipressin in improving renal functions |
| Singh et al. 2012 | Forty-six patients with HRS type 1 were managed with terlipressin (group A, $N=23$) or noradrenaline (Group B, $N=23$) with albumin in a randomized controlled trial | HRS reversal could be achieved in 9 (39.1%) patients in group A and 10 (43.4%) patients in group B ($p=0.764$) | Noradrenaline is as safe and effective as terlipressin, but less expensive in the treatment of HRS and baseline CTP score is predictive of response |
| Boyer et al. 2016 REVERSE study | Patients were randomized to groups given intravenous terlipressin (1 mg, $n=97$) or placebo ($n=99$) every 6 h with concomitant albumin | HRS reversal was achieved in 23 of 97 (23.7%) patients receiving terlipressin vs 15 of 99 (15.2%) receiving placebo ($p=0.13$) | Terlipressin plus albumin was associated with greater improvement in renal function vs albumin alone in patients with cirrhosis and HRS-1 |
| Caraceni et al. ANSWER study | Patients were randomized to (SMT) or SMT plus HA (40 g twice weekly for 2 weeks, and then 40 g weekly) for up to 18 months | The incidence rate ratio of hepatorenal syndrome type 1 with its 95% CI was $<0.5$ indicating a significant reduction in the SMT plus HA group | Long-term albumin administration prolongs overall survival and acts as a disease-modifying treatment in patients with decompensated cirrhosis |
| Sanyal et al. REVERSE trial | Patients received intravenous terlipressin 1–2 mg every 6 h plus albumin or placebo plus albumin up to 14 days | HRS reversal was significantly more frequent with terlipressin vs. placebo (27% vs. 14%; $p=0.004$) | Terlipressin plus albumin resulted in a significantly higher rate of HRS reversal vs. albumin alone in patients with HRS-1 |
| Cavallin et al. Italian study group | To compare the effectiveness of terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of HRS | There was a higher rate of recovery of renal function in thr TERLI group (19/27, 70.4%) compared to the MID/OCT group (6/21, 28.6%) | Terlipressin plus albumin is more effective than midodrine and octreotide plus albumin in improving renal function in patients with HRS |
| Arora et al. 2019. ILBS study group | Patients with ACLF and HRS were randomized to albumin with infusion of terlipressin or noradrenaline | Infusion of terlipressin gives earlier and higher response than noradrenaline, with improved survival in ACLF patients with HRS-AKI | Compared to noradrenaline, terlipressin achieved greater day 4 and day 7 response and reversal of HRS |
| Wong et al. CONFIRM investigators | Patients were randomly assigned in a 2:1 ratio to receive terlipressin plus albumin or placebo plus albumin | Reversal of HRS was reported in 63 patients (32%) in the terlipressin group and 17 patients (17%) in the placebo group ($p=0.006$) | Terlipressin and albumin infusion was more effective than placebo in improving renal function |
| China et al. ATTIRE investigators | Patients were randomly assigned to targeted 20% albumin solution arm till 14 days or discharge and in the standard care arm | Kidney dysfunction occurred in (10.5%) the albumin group and (14.4%) in the standard care group | Albumin infusions to a target of 30 g/l or more was not more beneficial than the current standard care |

**Table 5** (continued)

| Study | Methodology | Renal dysfunction | Conclusion |
|---|---|---|---|
| Sola et al. MACHT investigators | Patients were randomly assigned to receive midodrine (15–30 mg/day) and albumin (40 g/15 days) or matching placebos for 1 year | Treatment with midodrine and albumin was associated with HRS reversal and decrease in plasma renin activity and aldosterone compared to placebo | Treatment with midodrine and albumin slightly suppressed the activity of vasoconstrictor systems |

Studies of albumin in cirrhosis

*SMT* standard medical therapy, *HA* human albumin, *HRS* hepatorenal syndrome, *Terli* terlipressin, *Mid* midodrine, *OCT* octreotide

in MAP by more than 5 mm of Hg at day 3 had significantly higher HRS reversal (73% vs. 36%; $p=0.037$) [154]. A pooled analysis of 21 studies including 501 patients explored the relationship of increase in MAP with HRS reversal using different vasoconstrictors (terlipressin, ornipressin, midodrine, octreotide or norepinephrine). The authors observed that a decline in serum creatinine was strongly associated with the increase in MAP, but not with improvement in urine output [155]. These associations were more strongly observed when the analysis was restricted to RCTs. However, studies were not performed in patients with ACLF. Zheng et al. showed a drop in MAP of ≥ 9.5 mmHg was an independent predictor of HRS in a large cohort of HBV ACLF patients [156]. In a large randomized controlled trial performed in critically ill patients with cirrhosis, the TARGET-C, a higher target MAP (80–85 mm of Hg) [157] was associated with improved renal outcomes and better tolerance to dialysis, but at the cost of more adverse events. Higher target MAP did not confer survival benefit at 28 days compared to the lower target group (60–65 mm of Hg). The use of terlipressin, higher SOFA scores, and hypernatremia were identified as independent predictors of adverse events. In the randomized controlled trial by Arora et al., adverse events necessitated protocol discontinuation in 15% of patients. A higher target MAP of 80–85 mm of Hg is preferable during the management of HRS-AKI in patients with ACLF; however, close monitoring of adverse events should be pursued especially in patients receiving terlipressin.

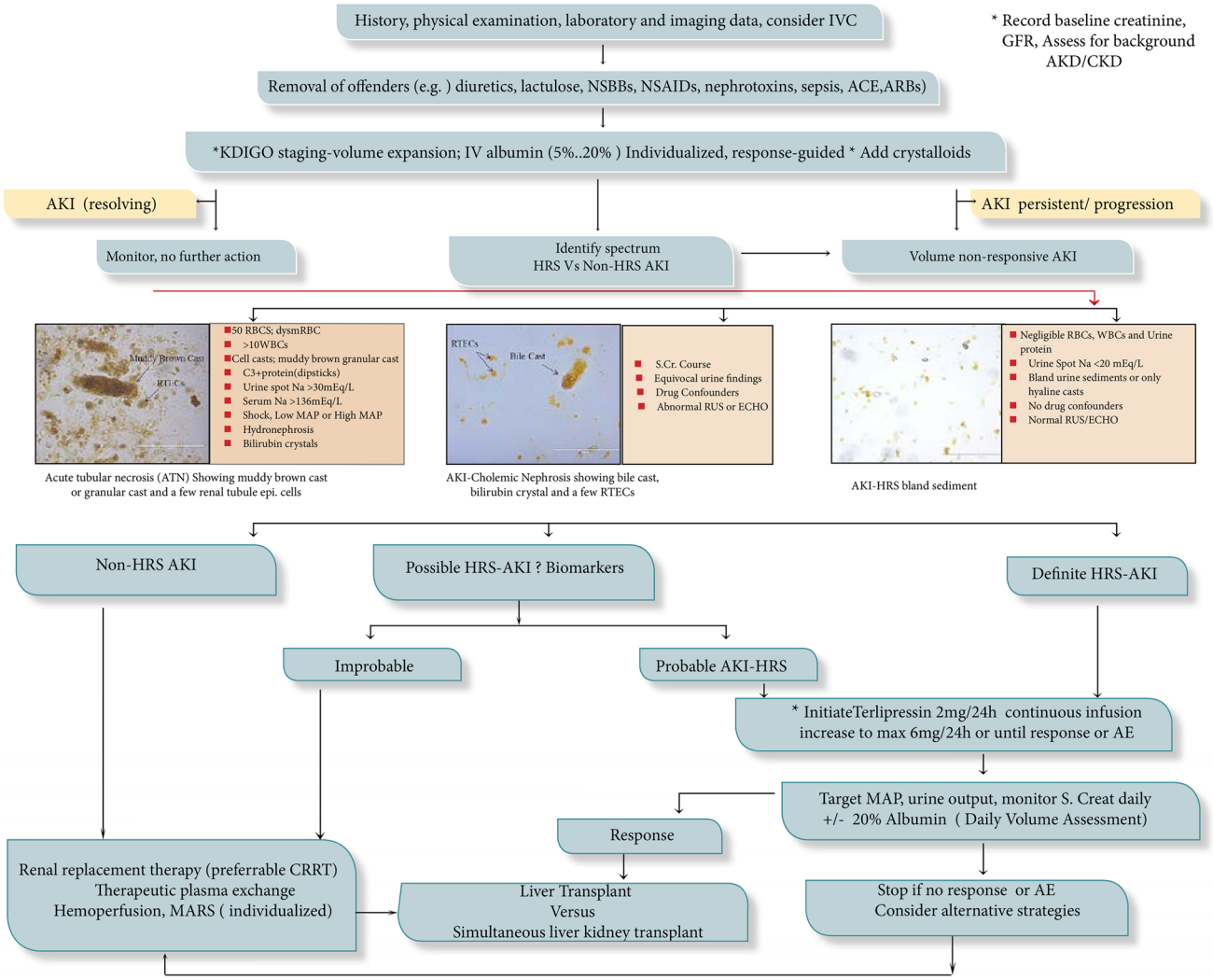
### Statement

A higher target MAP is preferable over a lower target. Higher MAP improves renal perfusion by improving the splanchnic and systemic vasodilatation. However, close monitoring for adverse events should be pursued in these patients, especially those being treated with terlipressin. **[LoE4, strong recommendation, consensus 91%].**

### Recommendation

A minimum target MAP of 65–70 mmHg during the management of HRS-AKI in patients with ACLF is recommended. [**LoE4, strong recommendation, consensus 85%].**

Terlipressin should be initiated at 2 mg as a continuous infusion over 24 h with the escalation of the dose every 6 h to a max. of 6 mg/day or the development of adverse events [158]. The dose escalation should be guided by MAP (target above 65–70 mm of Hg), urine output assessment every 6 h (target > 0.5 ml/kg/h), and/or daily monitoring of sCr (more than 25% reduction from baseline) to classify drug response. Patients who achieve the target MAP of 80–85 mm Hg, but have not achieved the goals of urine output or sCr or develop




The algorithm depicts the proposed strategy for the management of acute kidney injury in acute on chronic liver failure. The designed algorithm is not a strict guideline, but can be considered for better reasoning and decision-making while managing and treating such patients. Initially, using the baseline estimated glomerular filtration rate, urine microscopy, imaging should be evaluated to understand the status of background kidney disease. The baseline serum creatinine and/ or urine output should be recorded for staging the AKI. The initial management should be to assess for all risk factors (as listed in Fig. 5) and checking the volume status followed by volume resuscitation using 20% or 25% albumin therapy versus use of a 4% or 5% albumin in patients with shock who are volume depleted. In such patients, crystalloids can also be added if required and blood components if patients have hemorrhagic shock. In patients admitted to the intensive care unit, a cardiac echocardiogram, intraabdominal pressure monitoring, and renal Doppler (wherever feasible) may be incorporated as a part of routine care. If patient's AKI seems to improve, no further treatment is required. However, if the patient has AKI persistence/progression (as defined in definitions), a urine microscopy should be performed to differentiate hepatorenal syndrome versus acute tubular necrosis. The presence of bile cast or bilirubin crystals should point toward the presence of cholemic nephropathy. Patients with definite diagnosis of HRS-AKI should be managed with continuous infusion or terlipressin (as first choice in the absence of any contraindications) or norepinephrine. In these intravenous therapies, the dose and administration of albumin therapy should be decided dynamically based on the volume status. In patients with non-response to terlipressin or development of adverse events, terlipressin should be discontinued and alternative modalities (renal replacement) should be considered on a case-to-case basis. In patients with non-HRS AKI, biomarkers can be used as a guide to decide the predicted response to terlipressin versus alternative modalities of renal or extracorporeal liver support. Therapeutic plasma exchange may be considered; however, the data is limited. An early liver transplant should be considered in patients with resolving AKI, while the decision for liver transplant alone versus simultaneous liver kidney transplant in patients with non-HRS-AKI or stage 3 AKI should be decided based on a multidisciplinary team. AIN, acute interstitial nephritis; AGN, acute glomerulonephritis; ECHOC, echocardiogram; HRS-1, hepatorenal syndrome type 1; IV, intravenous; IVCd, inferior vena cava diameter; NSAIDs, nonsteroidal anti-inflammatory drugs; NSBBs, non-selective beta blockers; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers OU, obstructive uropathy; PO, per os; RBCs, red blood cells; RUS, renal ultrasound; sCr, serum creatinine; Na, sodium; WBCs, white blood cells; KDIGO, Kidney Disease Improving Global Outcome; MAP, mean arterial pressure; CKD, chronic kidney disease; AKI, acute kidney injury

adverse events should be considered non-responders to terlipressin and further dose escalation of terlipressin should not be performed in these patients and alternative strategies should be considered for HRS-AKI management. The post hoc analysis from the CONFIRM trial demonstrated higher renal recovery and decreased need for dialysis both pre- and post-liver transplant in patients who received terlipressin compared to standard medical treatment Table 5 [159–166].

#### Recommendation 5a

Considering a high probability of adverse events, terlipressin should be initiated as an infusion at a dose of 2 mg/24 h with escalation to a maximum of 6 mg/day in the management of HRS-AKI. **[LOE4, strong recommendation, consensus 97%].**

#### Recommendation 5b

Measurement of MAP and urine output at least every 6 h along with daily measurement of sCr should be used for guiding the dose of terlipressin escalation during the management of HRS-AKI in patients with ACLF. [**LOE2, strong recommendation, consensus 97%].**

#### Recommendation 5c

Patients who achieve the target MAP of 80–85 mm of Hg, but have no improvement in urine output, or a reduction in sCr by 25% despite the maximal dose of terlipressin or develop adverse events should be considered as non-responders to terlipressin. In such patients, terlipressin should be discontinued and alternative strategies considered. **[LOE5, strong recommendation, consensus 85%].**

#### Recommendation 5d

Patients with a one-stage reduction in AKI (based on revised criteria of AKI as detailed above incorporating urine output or sCr) should be considered as responders to terlipressin. Terlipressin in these patients should be continued until complete renal recovery or until receipt of liver transplant. [**LoE5, strong recommendation, consensus 91%**].

## Section IVC: Renal replacement therapy in AKI in ACLF

### What initiation strategy, modality, and dose should be considered for renal replacement therapy in patients with ACLF and AKI stage 3?

The debate on timing, modality, and dose of dialysis has been ongoing and still there is a lack of consensus [167, 168]. Most studies exploring the dialysis strategy have excluded patients with decompensated cirrhosis. In the artificial kidney initiation in kidney injury trial (AKIKI), the early strategy defined as dialysis initiation within 6 h of meeting KDIGO stage 3 was comparable to a delayed strategy [169]. The post hoc analysis in the subset of patients with severe sepsis, acute respiratory distress syndrome also failed to show the benefits of early initiation [170]. In the most recent meta-analysis, including 11 RCTs comparing the effects of early and late RRT on AKI patients, failed to show improvement in 28-day mortality by early initiation [38.1% (431/1131) and 40.7% (453/1111] compared to late initiation, respectively. A total of 1131 and 1111 AKI patients assigned to early and late RRT strategies, respectively, were enrolled in this meta-analysis [171]. Further, there was no significant difference between groups in terms of RRT dependence in survivors on day 28 (RR, 0.90; 95% CI, 0.67–1.25, I 2 = 0%) and recovery of renal function (RR, 1.03; 95% CI 0.89–1.19, I 2 = 56%). In an individual patient data meta-analysis, early initiation of dialysis was not associated with improved outcomes. However, in all the studies, the type of dialysis modality was decided by the attending clinician and population of patients and the definitions for early dialysis initiation were very heterogenous [172]. On the contrary, a large single-center trial, the ELAIN trial, showed the impact of early strategy in improving both short- and long-term recovery of renal functions. In the trial, the study group comprised a homogenous set of patients and all patients underwent continuous RRT (CRRT), which was initiated when patients met KDIGO stage 2 and they also used urine NGAL as a biomarker for guiding the dialysis initiation [168]. Patients with cirrhosis are a distinct group with marked hemodynamic alterations. In an open-label randomized controlled trial, early initiation of CRRT in patients with ACLF with septic shock and stage 3 AKI showed the benefits in achieving a hemodynamic response and trend toward improved transplant-free 28-day survival [173]. Patients in the early group were initiated on CRRT within 24 h of the onset of shock versus the late group (CRRT when the patient met the absolute criteria. Renal recovery was also more frequent in the early CRRT group. Patients with cirrhosis more frequently develop intradialytic hypotension during dialysis and this is more frequent with intermittent modes of dialysis. SLED is a hybrid modality of dialysis which is currently used as an effective alternative to CRRT in resource-constrained countries [174, 175]. In the TARGET-C trial, a higher incidence of hypotension was demonstrated with SLED compared to CRRT, even though CRRT was performed in the hemodynamically unstable group [157]. Although the data from general critically ill population have not shown benefits of CRRT over intermittent modes of dialysis, all experts believed CRRT to be preferable compared to intermittent modes of dialysis in ACLF patients. However, the decisions would also be

guided by the resource availability, expertise, and cost of the therapy. The data on the exact dose of dialysis is also limited in patients with cirrhosis. In critically ill patients, the evidence has not shown any difference between a lower dose (20–25 ml/kg/h) compared to a higher dose strategy [176, 178]. However, the higher dose CRRT has been reported to be associated with better ammonia clearance in patients with ALF and decompensated cirrhosis [179–184]. The higher dose could be considered in the subset of patients wherein it is required. Also, close monitoring and recording of the actual delivered dose should be pursued in the management of these patients [176, 177].

**Statement** Pre-emptive initiation of RRT may be required in patients with ACLF with stage 3 AKI with progression or non-response to vasoconstrictors within the first 12–24 h. [**LoE5, strong recommendation, consensus 91%**].

**Recommendation 6a** Patients with ACLF with stage 3 AKI with progression or non-response to vasoconstrictors should be considered for RRT. **[LoE5, weak recommendation, consensus 85%].**

**Recommendation 6b** Considering systemic inflammation as the key driver of AKI in patients with ACLF and marked circulatory dysfunction, CRRT could be preferred over the intermittent modes of dialysis. However, the decisions would also be guided by the resource availability, expertise, and cost of the therapy. [**LoE5, strong recommendation, consensus 97%**].

**Recommendation 6c** CRRT may be preferred over the intermittent modes of dialysis in patients with ACLF and stage 3 AKI. [**LoE5, strong recommendation, consensus 97%**] [**LoE5, strong recommendation, consensus 100%**].

**Recommendation 6d** **A** lower dose of 20–25 ml/kg/h over the higher dose as an initial strategy in the management of AKI stage 3 in patients with ACLF is recommended. Higher doses can be individualized in patients with non-response to the lower dose. **[LoE 5, strong recommendation, consensus 100%].**

### Can citrate anticoagulation be safely used in patients with ACLF on CRRT?

The use of citrate as anticoagulation in CRRT is fraught with the risk of citrate toxicity. In patients with liver failure, there are concerns about reduced metabolism and systemic accumulation and toxicity. This is usually manifested in these patients as either metabolic alkalosis or acidosis, coagulopathy, and an increase in the total calcium/ ionic calcium. In a study by Schultheiss and colleagues, the safety of regional citrate anticoagulation (RCA) was demonstrated in patients with liver failure. They found that the ratio of total calcium to ionic calcium > 2.5 was an independent predictor of 28-day mortality. Patients with arterial lactate > 3.5 mmol/L and those with deranged coagulation were more likely to have impaired citrate metabolism and toxicity [185]. In a systematic review and meta-analysis which included 10 observational studies with 1241 liver dysfunction patients to analyze the safety of RCA, the pooled rate of citrate accumulation and bleeding was seen to be 12% and 5% respectively. A significant increase in total/ionic calcium and metabolic alkalosis without any significant increase in serum citrate was noted. There was no significant increase in the serum total bilirubin and arterial lactate in liver failure patients compared to non-liver failure patients [186, 187].

**Statement** The use of RCA may be used in patients with ACLF and AKI stage 3 on CRRT, however, based on the current evidence cannot be routinely recommended. A close monitoring of the total calcium to ionic calcium ratio should be performed to determine citrate accumulation. More studies are warranted on the safety of RCA compared to no anticoagulation in ACLF patients with AKI. [**LoE4, strong recommendation, consensus 97%**].

**Recommendation 6e** RCA can be used in patients with ACLF on CRRT, with close monitoring of acid base status and total calcium to ionic calcium to detect citrate accumulation. [**LoE4, weak recommendation, consensus 97%**].

### What protocols of weaning should be considered in patients with ACLF on RRT?

Studies performed on patients with decompensated cirrhosis and ACLF have demonstrated worse outcomes on dialysis. The decisions of stopping or weaning a patient from dialysis is an area which needs investigation. There are no controlled studies evaluating weaning protocols for dialysis in patients with ACLF and limited data exists. Dialysis can be used only for a brief period until LT and/or spontaneous renal recovery. In a study by Staufer and colleagues, evaluating patients with cirrhosis requiring RRT in the ICU, a high mortality at 28 day-, 90 day-, and 1 year of 83%, 91%, and 92%, respectively, was observed compared to 30%, 43%, and 50%, respectively, in the group of patients who did not receive RRT. SOFA scores within 24 h prior to RRT showed good discriminant power to predict ICU mortality. Patients requiring RRT with ≥ 5 organ failures assessed by CLIF-SOFA at any time point showed 100% ICU mortality. Only 13% of patients with RRT showed renal recovery, while 14% of patients could be bridged to LT. In these patients requiring acute RRT in ICU, a CLIF-C-ACLF

above 59.5 calculated at 48 h after starting RRT was the best predictor of ICU mortality (AUROC 0.87) regardless of liver transplant options [188]. This could be used as a guide to terminate dialysis in these patients. Prolonged dialysis may be associated with high costs and could be futile in the absence of a proactive liver transplant. Therefore, weaning from dialysis should be proactively pursued in patients with ACLF if they achieve renal recovery or until a liver or simultaneous-liver kidney transplant. Futility of RRT should be considered in patients without options of transplant and the goals of withdrawing renal support proactively discussed in a multidisciplinary meeting [189–191].

**Statement** Weaning for dialysis should be actively pursued in patients with ACLF, AKI 3 on dialysis. **[LoE5, strong recommendation, consensus 97%].**

**Recommendation 6f** Patients should be actively weaned from dialysis if they achieve renal recovery or if the patient is not a candidate for LT. **[LoE5, strong recommendation, consensus 97%].**

## Section IVD: Liver transplant in patients with ACLF and AKI

Kidneys are considered as an organ of utility by APASL. This is because the presence of kidney dysfunction or failure is not a contraindication for a LT. Early LT can improve outcomes in the presence of HRS-AKI. In a recent investigation by Zhang and colleagues wherein the benefits of early LT were demonstrated, kidney involvement was observed in 80.5% and 81.7% of patients with three and three to six organ failures [192]. Gousssous et al. studied patients with ACLF, 77% with grade 3 ACLF, and the proportion of patients with kidney failure was found to be different (82.6% vs. 86.2%) for patients who were transplanted versus those not, respectively [193]. In another large cohort, wherein outcomes of emergency transplants were evaluated, patients on RRT were considered and had excellent outcomes [194]. However, multicentric data from the CANONIC investigator's 1-year post-LT survival of patients with ACLF showed the following factors to be independently associated with post-LT mortality, i.e., lactate levels > 4 mmol/L need for RRT at LT and infections with multidrug-resistant organisms while on the waiting list [195]. Interestingly, the data from the Asia–pacific showed almost two-thirds of patients of ACLF are ineligible for a LT because of infections and severe renal involvement requiring RRT [196]. Together, the data suggest the high frequency of renal involvement and mixed outcomes with an emergency LT in patients with ACLF. In another recent study, Sundaram et al. showed renal involvement as an independent predictor of worse outcomes in patients after LT [197]. The course of organ failures, especially the kidneys and other organ failures in the intensive care unit, is another determinant of outcomes. Resolution of organ failures with an effective and appropriate infection management are associated with improved outcomes [198]. Gustot et al. showed patients with persistence or progression of ACLF grade 3 with four or more organ failures on day 3–7 of the ICU stay have significantly worse outcomes and are considered futile [199]. It is difficult to assess the impact of AKI 3 at the time of LT on post-LT outcomes such as infections, hospital stay, and early mortality, as generally patients with ACLF suffer from multiorgan dysfunction. Patients with ACLF 3 have higher complications after LT [200, 201]. Dialysis or anuria prior to LT is not reported by the majority of ACLF studies, as these patients are generally not taken up for LT alone in the living donor LT setting. In the deceased donor, LT studies have reported renal failure as defined by ACLF CLIF OF/modified SOFA (creatinine > 2 mg/dl) with no further attempt to subclassify AKI [202]. The ELITA study reported the use of RRT as an independent predictor of worse outcomes post-LT [195]. Dialysis has been shown to be one of the predictors of mortality after LT in non-ACLF patients [199]. Only a few studies have described the outcomes of RRT at the time of LT. Patients with ACLF may have poor renal outcomes after LT also. Agbim et al. reported lower eGFR and a higher need for RRT in the ACLF group as compared to the no-ACLF group [202].

The presence of acute tubular necrosis compared to HRS is associated with inferior outcomes and higher progression to CKD post-transplantation [200]. Patients requiring RRT beyond 30 days have higher chances of non-recovery and should ideally be considered for a simultaneous liver kidney transplant. Goosmann et al. studied the development of CKD post-transplantation. The prevalence of renal involvement was 90% in their cohort. They observed a higher prevalence of CKD stage 3 or more in ACLF LT recipients after 12 months ($p = 0.03$). Further, the prevalence of CKD ≥ grade 3 increased to 73% in the non-ACLF LT group compared to 82% in the ACLF LT group ($p$ = n.s.) after 5 years [203]. Yazava et al. compared 356 non-ACLF patients with 60 patients with ACLF. The patients with ACLF and eGFR < 30 mL/min/1.73 $m^2$ at LT had significantly higher composite kidney outcomes (eGFR < 15 mL/min/1.73 $m.^2$ or need for dialysis) [45]. Other factors which, even though not prospectively studied but are relevant, include recipient age > 65 years, fraility, active alcohol intake, and duration of mechanical ventilation in patients in the ICU. The impact of comorbid diseases, cardiac and diabetes, which is associated with higher prevalence of underlying significant renal dysfunction could also impact long-term renal outcomes [204].

#### Statement 1a

The presence of stage 1 or 2 AKI if non-resolving should not be a contraindication for expedited liver transplant. [**LoE4, strong recommendation, consensus 94%].**

#### Recommendation1a

ACLF patients with stage 1 or 2 AKI even if non-resolving should be considered for an expedited liver transplant. [**LoE4, strong recommendation, consensus 94%**].

#### Statement 1b

Patients with ACLF with AKI on dialysis, with a diagnosis of acute tubular necrosis, and oliguria, and those with other organ failures have worse outcomes. In such patients, a multidisciplinary team and decision-making should be performed for considering liver transplant alone versus simultaneous liver–kidney transplant. This should be performed on a case-to-case basis. [**LoE4, weak recommendation, consensus 97%].**

#### Recommendation 1b

The decision for liver transplant alone versus simultaneous liver–kidney transplant should be individualized for patients with ACLF and AKI with a diagnosis of acute tubular necrosis or oliguria and on RRT. [**LoE4, strong recommendation, consensus 97%**].

## Section V": Care of post-discharge AKI in ACLF

### Statement

Considering a higher prevalence of structural AKI and non-response to therapies, patients with ACLF post-discharge should be followed closely for the development of acute kidney disease or progression to CKD. [**LoE5, strong recommendation, consensus 97%**].

### Recommendation

A close monitoring of renal functions post-discharge in patients with ACLF who have recovered from AKI is recommended. [**LoE5, strong recommendation, consensus 97%).**

## Section VI: AKI on CKD in ACLF

Napoleone and colleagues [205], investigated the patterns of kidney dysfunction and outcomes in patients with acute decompensation (AD) of cirrhosis, with or without ACLF. They performed a prospective cohort study including 639 admissions for acute decompensation (232 with ACLF; 407 without) in 518 patients. Data were collected at admission and during hospitalization, and patients were followed up for 3 months. Urine samples were analyzed for kidney biomarkers. Most patients with ACLF (92%) had associated AKI, in most cases without previous CKD, whereas some had AKI on CKD (70% and 22%, respectively). The prevalence of AKI in patients without ACLF was 35% ($p < 0.001$ vs. ACLF). The frequency of CKD alone was low and similar in both groups (4% and 3%, respectively); only a few patients with ACLF (4%) had no kidney dysfunction. They further observed that AKI in ACLF was associated with poor patient outcomes compared with no ACLF (AKI resolution: 54% vs. 89%; 3-month survival: 51% vs. 86%, respectively; $p < 0.001$ for both). The independent predictive factors of 3-month survival were MELD–Na, ACLF status, and urine NGAL. Intriguingly, patients with ACLF associated with AKI on CKD had better survival compared to those with AKI without CKD (68% vs. 31%, respectively; $p \leq 0.001$). The authors concluded that AKI is almost universal in patients with ACLF, sometimes associated with CKD, whereas CKD alone is uncommon. The prognosis of AKI depends on ACLF status. AKI on CKD was associated with better kidney and patient outcomes compared with those of AKI alone, with a lower rate of progression of AKI and a higher survival rate. The reason for these paradoxical findings is unknown and deserves investigation.

### Statement

The prevalence of CKD alone is uncommon in ACLF patients and occurs mostly concomitantly with AKI. Limited data suggests that the presence of CKD does not confer worse outcomes in these patients. However, the impact of underlying CKD in patients with ACLF needs further prospective studies. [**LoE4, WEAK RECOMMENDATION, CONSENSUS 79%**].

## Section VII: Nutrition in AKI

### Recommendation 1a

Protein restriction should not be pursued in patients with ACLF and AKI. [**LoE5, weak recommendation, consensus 97%**].

### Recommendation 1b

Patients with ACLF with AKI on CRRT have a high catabolic state and 1.5–2 gm/kg of protein should be prescribed for such patients. [**LoE5, weak recommendation, consensus 97%].**

## Limitations

The current practise guidelines are an endeavor for framing an approach toward the diagnosis and management of AKI in ACLF. The consensus document is based on the opinions of experts involved in the management of this very sick group of patients. However, the major limitation is the lack of robust data supporting various recommendations. This also highlights the need for developing randomized clinical trials and multicentric studies exploring most of these clinical questions which are faced day to day in the management of AKI in ACLF patients.

## Summary

The current consensus document is the guidance on clinical management of AKI in ACLF patients. The guidelines have been developed by involving experts across the globe dealing with managing AKI in ACLF patients. AKI is the most frequent extrahepatic organ involved in these patients and also follows a rapidly progressive course. Pathophysiologically, AKI is dominated by a higher prevalence of structural kidney damage secondary to circulatory dysfunction, acute worsening of portal hypertension, and intense systemic inflammation causing mitochondrial dysfunction. Prevention is the key, and all efforts should be made to avoid nephrotoxic agents which could precipitate AKI in patients with ACLF. Appropriate maintenance of MAP and regular monitoring of renal functions should be instituted for early detection of AKI. Whether long-term use of albumin could be useful in patients with ACLF in preventing AKI remains to be investigated.

## Research priorities

Patients with ACLF have a rapidly progressive AKI which is more often structural and responds poorly to the current treatment modalities. CN, which is caused by injury secondary to bile acids, and high bilirubin in the presence of systemic inflammation is more often encountered in these patients with ACLF. CN is difficult to diagnose due to lack of a histological diagnosis. Prospective studies looking at pathophysiology, role of non-invasive biomarkers in diagnosing CN, its differentiation from ATN, and the role of extracorporeal therapies are needed. Similarly, large prospective studies are required for exploring the role of biomarkers in the diagnosis of subclinical AKI, predicting the course, need of RRT, and recovery from RRT in ACLF patients with AKI. Biomarkers of host response identifying adaptive versus a maladaptive repair could risk stratify patients developing AKD or CKD after an AKI episode. The fluid management protocols should be guided by dynamic indices (esp. the lung ultrasound) considering higher risk of these patients getting cardiopulmonary complications. Also, early initiation of albumin in stage 1 AKI and initiation of vasoconstrictors based on dynamic assessment could improve the overall outcomes. Extracorporeal therapies, for instance therapeutic plasma exchange and cytokine hemadsorption by ameliorating systemic inflammation, could be promising adjunctive strategy in the management of AKI which should be explored in multicentric randomized controlled trials. For the same reason, CRRT could be a better modality compared to intermittent modes of dialysis, which should be initiated timely in non-responders to terlipressin or in ATN patients. Natural history and mechanistic studies, exploring transition of AKI to AKD or CKD in ACLF patients, are an unmet need. Considering the poor outcomes and rapid progression of stage 3 AKI, studies on whether routine admission of these patients to the intensive care unit enabling intensive monitoring of the acid–base, urine output, and intraabdominal pressure could improve overall outcomes are needed. Whether outcomes of ACLF patients on dialysis with or without oliguria are different needs to be studied. Patient selection for liver transplant versus a simultaneous liver–kidney transplant is also not known.. Outcomes of liver transplant alone in ACLF patients on a short duration of dialysis are required from prospective controlled studies from high-volume centers. Last but not the least, models predicting futility of liver transplant, dialysis and intensive care unit are urgently needed in these patients. The current initiative by APASL shows the vacuum in the management of AKI in ACLF patients. We would encourage focused studies exploring these aspects

which enable the current consensus to be updated by good quality evidence in the near future.

**Author contributions** Rakhi Maiwall, Satender Pal Singh, Phool Chand, and Omkar Rudra drafted the manuscript. Paolo Angeli, Richard Moreau, Aleksander Krag, Ashwani K. Singal, Manoj Kumar Sharma, Subhash Gupta, Shalimar, Anand Kulkarni, and Nipun Verma provided inputs and edited and critically revised the manuscript. Virender Singh, S.S.Tan, Puneet Puri, Mamun Mahtab, George Lau, Qin Ning, P.N.Rao, Dharmesh Kapoor, Ajay Duseja, Manav Wadhawan, Dinesh Jothimani, Sanjiv Saigal, Sunil Taneja, Akash Shukla, Pankaj Puri, Deepak Govil, Gaurav Pandey, Kaushal Madan, Sunil Taneja, C.E.Eapen, Jaya Benjamin, Ashok Chowdhury, Shweta Singh, Vaishali Salao, Jin Mo Yang, Saeed Hamid, Sanjiv Jasuja, Madund A Niriella, Harsh Vardhan Tevethia, Vinod Arora, R.P.Mathur, Akash Roy, Ankur Jindal, Neeraj Saraf, Arka De, Narendra S Choudhury, and Rohit Mehtani reviewed and approved the manuscript. Shiv Kumar Sarin reviewed the manuscript, critically revised the manuscript, and approved it.

**Funding** None.

## Declarations

**Conflict of interest** None of the authors (Rakhi Maiwall, Satender Pal Singh, Paolo Angeli, Richard Moreau, Aleksander Krag, Virender Singh, Ashwani K. Singal, S. S. Tan, Puneet Puri, Mamun Mahtab, George Lau, Qin Ning, Manoj Kumar Sharma, P. N. Rao, Dharmesh Kapoor, Subhash Gupta, Ajay Duseja, Manav Wadhawan, Dinesh Jothimani, Sanjiv Saigal, Sunil Taneja, Akash Shukla, Pankaj Puri, Deepak Govil, Gaurav Pandey, Kaushal Madan, C. E. Eapen, Jaya Benjamin, Ashok Chowdhury, Shweta Singh, Vaishali Salao, Jin Mo Yang, Saeed Hamid, Shalimar, Sanjiv Jasuja, Anand V. Kulkarni, Madund A Niriella, Harsh Vardhan Tevethia, Vinod Arora, R. P. Mathur, Akash Roy, Ankur Jindal, Neeraj Saraf, Nipun Verma, Arka De, Narendra S Choudhary, Rohit Mehtani, Phool Chand, Omkar Rudra, Shiv Kumar Sarin) have conflict of interest pertaining to the current work.

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