TABLE 9 Future research directions for the management of critically ill patients with cirrhosis and/or ACLF

Overall	Uniform definition of ACLF that can be applicable worldwide Appropriate duration of onset to define ACLF Standard management protocol for ACLF targeted at early diagnosis and reversal of precipitating events and organ failures Objective outcomes (e.g., 1- or 3-month mortality) that are standardized
Prognosis	Validated clinical scoring systems to assess severity of ACLF early in the clinical presentation Scores that predict future decompensation and not simply reflect current critical illness Establishing interval for serial risk assessment Role of biomarkers such as NGAL or cystatin C[274,275] in prediction of short-term mortality Role of other inflammatory biomarkers,[276] serum metabolites,[277,278] and markers of dysbiosis[279,280] in prediction of short-term mortality
Brain failure	Role of biomarkers for prediction and specific diagnosis of HE-related brain failure Newer therapeutic options that maximize pain control without sedation
Kidney Failure	Role of biomarkers (NGAL, kidney injury molecule 1, cystatin C, IL-18, liver fatty-acid binding protein) to differentiate the causes of AKI[281–283] and assess response to treatment Development of newer classes of drugs such as renal vasodilators in combination with systemic vasoconstrictors[284]
Infection	Novel approaches to identify MDR and fungal organisms earlier in patients with cirrhosis Culture-independent identification of causative organisms using rapid PCR "syndrome panels" and metagenomics Studies to assess the optimal antibiotic therapy for SBP prophylaxis after MDR infections Role of microbiome alteration and outcomes after transplantation[285–287]
Coagulopathy	Utilization of viscoelastic testing (TEG/ROTEM) in larger populations of critically ill patients with cirrhosis
Nutrition	Optimal caloric and protein requirements in critically ill patients with cirrhosis
Cardiovascular	Optimal MAP threshold and vasopressor choice Type, quantity, and target of albumin administration (serum albumin level vs. physiologic measures) Overall resuscitation strategies
Pulmonary	Utility of indices predicting potential failure of noninvasive interventions and the need for escalation to invasive mechanical ventilation Potential benefits of low tidal volume and low PEEP strategies in mechanical ventilation on cardiopulmonary function and survival in patients with ACLF Evidence-based criteria (e.g., $PaO_2/FiO_2 < 150$ mm Hg) regarding objective respiratory parameters that would preclude transplant[227]
Transplantation	Predictive models for LT candidacy and futility Protocolized assessment, management, and evaluation of potential LT candidates Policies regarding SLKT in critically ill patients with cirrhosis/ACLF
Palliative	Incorporation of palliative care principles into hepatology training Developments of liver-specific hospice to expand its acceptance and use for inpatient and outpatients with cirrhosis

Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; FiO_2, fraction of inspired oxygen; LT, liver transplantation; MAP, mean arterial pressure; MDR, multidrug resistant; NGAL, neutrophil gelatinase-associated lipocalin; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; ROTEM, rotational thromboelastometry; SBP, spontaneous bacterial peritonitis; SLKT, simultaneous liver–kidney transplant; TEG, thromboelastography.

and risk of death. Therefore, palliative care consultation should be incorporated into the management of critically ill patients with cirrhosis (Table S4, http://links.lww.com/HEP/I105). Although palliative care remains underutilized,[246–251] it is associated with a lower procedure burden and cost saving of ~$10,000 per patient with end-stage liver disease.[247,252] In the Nationwide Readmissions Database, those who received a palliative care consult had ~50% lower rates of readmission, a shorter length of stay, and inpatient healthcare cost savings.[253] In another study, palliative care consult cut readmissions by two thirds and doubled the chance of hospice discharge.[246] Even when palliative care or hospice are consulted, it most often occurs late.[248–250,254] In contrast to current practice, a survey found that patients with cirrhosis prefer to undertake advanced care planning before the onset of decompensation.[255] Higher readmission at the end of life and in-hospital death combined with patient preferences for earlier advanced care planning should serve as a call to action for the hepatology community to engage palliative care sooner but certainly for all patients at ACLF diagnosis or ICU admission.

Quality palliative care

In 2017, an expert panel developed 19 quality indicators for palliative care of patients with end-stage liver disease.[256] Notable quality indicators relevant to patients with ACLF that were infrequently achieved (< 20%) included transfer of care, de-escalation orders from one hospital to another, goals of care discussion for patients with end-stage liver disease, being