# Appendix Table 1. List of PICO questions

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| **CARDIOVASCULAR** |
| 1. In critically ill patients with ALF or ACLF, should we recommend using hydroxyethyl starch or gelatin for initial resuscitation versus crystalloid solutions
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure | Hydroxyethyl starch or gelatin for initial resuscitation | Crystalloid solution for initial resuscitation | MortalityAcute Kidney InjuryOther organ failures |
| 1. In critically ill patients with ALF or ACLF, should we recommend using albumin for resuscitation versus other fluids
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure | Albumin for resuscitation | Non-albumin fluid for resuscitation | MortalityAcute Kidney InjuryOrgan Failure |
| 1. In critically ill patients with ALF or ACLF, should we recommend targeting mean arterial pressure of 65
 |
| Population | Intervention | Comparator  | Outcome(s) |
| Critically ill patients with liver failure | Mean Arterial Pressure Target of 65 mm Hg | Mean arterial pressure target less than 65 mm Hg or greater than 65 mm Hg | MortalityAcute Kidney InjuryOrgan Failure |
| 1. In critically ill patients with ALF or ACLF who remain hypotensive despite fluid resuscitation, should we recommend monitoring blood pressure with an arterial line
 |
| Population | Intervention | Comparator | Outcomes(s) |
| Critically ill patients with liver failure | Blood pressure monitoring with invasive arterial catheter | Blood pressure monitoring without invasive arterial catheter | MortalityOrgan failureCatheter related complications including infections |
| 1. In critically ill patients with ALF or ACLF who remain hypotensive despite fluid resuscitation, should we recommend invasive hemodynamic monitoring?
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure | Cardiovascular therapy guided by invasive hemodynamic monitoring | Cardiovascular therapy not guided by invasive hemodynamic monitoring | MortalityOrgan FailureCatheter related complications including arrhythmias and infections |
| 1. In critically ill patients with ALF or ACLF who remain hypotensive despite fluid resuscitation, should norepinephrine be used as a first-line vasopressor
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure | Norepinephrine as first line vasopressor for hypotension | Vasopressor other than norepinephrine as first line for hypotension | MortalityAcute Kidney InjuryOrgan Failure |
| 1. In critically ill patients with ALF or ACLF who remain hypotensive despite fluid resuscitation, should vasopressin be added to norepinephrine?
 |
| Population | Intervention | Comparator | Outcomes |
| Critically ill patients with liver failure | Vasopressin added to norepinephrine for hypotension despite fluid resuscitation  | Vasopressin not added to norepinephrine for hypotension despite fluid resuscitation | MortalityAcute Kidney InjuryOrgan Failure |
| **HEMATOLOGY** |
| 1. In critically ill patients with ALF or ACLF should we use INR, platelet, and fibrinogen versus viscoelastic testing (TEG/ROTEM) to assess for bleeding and thrombosis
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure | INR, platelet and/or fibrinogen to assess bleeding and thrombosis | Viscoelastic testing (TEG/ROTEM) to assess bleeding and thrombosis | MortalityBleedingThrombosisTransfusion of blood products |
| 1. In critically ill patients with ALF or ACLF who are not actively bleeding should we use a hemoglobin of 7 g/dL versus other levels as a threshold for initiation of packed red blood cell (PRBC) transfusion
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure without active bleeding | Hemoglobin of 7 g/dL as a threshold for initiation of PRBC transfusion | Hemoglobin of other than 7 g/dL as a threshold for initiation of PRBC transfusion | MortalityOrgan failureNumber of PRBC transfusionsTransfusion reactionsOther transfusion related adverse events |
| 1. In critically ill patients with ALF or ACLF should we use low molecular weight heparin (LMWH) or vitamin K antagonists versus conservative management for the treatment of venous thromboembolism
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure who develop venous thromboembolism | LMWH or vitamin K antagonist | Conservative management | MortalityMajor BleedingHeparin Induced thrombocytopenia |
| 1. In critically ill patients with ALF or ACLF should we use pharmacological prophylaxis (LMWH) versus mechanical prophylaxis (pneumatic compression stockings) for venous thromboembolism prophylaxis
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure | Pharmacological (LMWH) for venous thromboembolism prophylaxis | Mechanical (pneumatic compression stockings) for venous thromboembolism prophylaxis | MortalityOccurrence of venous thromboembolismMajor bleeding |
| 1. In critically ill patients with ALF or ACLF undergoing invasive or surgical procedures should we use INR, platelet count or fibrinogen level versus viscoelastic testing (TEG/ROTEM) to assess bleeding risk
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure undergoing invasive or surgical procedure | INR, platelet count and fibrinogen measurement | Viscoelastic testing (TEG/ROTEM) | MortalityBleedingThrombosisTransfusion of blood products |
| 1. In critically ill patients with ALF or ACLF should we use novel coagulation agents (prothrombin complexes, thrombopoetin receptor agonists, antifibrinolytics) to achieve pre-procedure or pre-surgery hematologic targets to reduce bleeding complications/transfusions
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure undergoing invasive or surgical procedures | Use of novel coagulation agents (prothrombin complexes, thrombopoetin receptor agonist, antifibrniolytics) | Not using novel coagulation agents | MortalityBleedingThrombosisTransfusion of blood products |
| **PULMONARY** |
| 1. In critically ill patients with ALF or ACLF and ARDS receiving mechanical ventilation should we use low tidal volume (< 6ml/kg PBW) versus high tidal volume (>8 ml/kg PBW)
 |
| Population | Intervention | Comparator | Outcomes(s) |
| Critically ill patients with liver failure receiving mechanical ventilation | Low tidal volume ventilation (< 6 ml/kg PBW) | High tidal volume (> 8 ml/kg PBW) | MortalityBarotraumaVentilator free daysOrgan Failure |
| 1. In critically ill patients with ALF or ACLF who develop ARDS should we use high PEEP versus low PEEP
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure who develop ARDS | High PEEP | Low PEEP | MortalityBarotraumaVentilator free daysIntracranial pressure |
| 1. In critically ill patients with chronic liver failure and portopulmonary hypertension should we use therapy targeted to pulmonary arterial hypertension
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with chronic liver failure and portopulmonary hypertension | Use of pulmonary arterial hypertension therapy | No use of pulmonary arterial hypertension therapy | MortalityLiver transplantation eligibilityHemodynamicsRight ventricular function |
| 1. In critically ill patients with chronic liver failure and hepatopulmonary syndrome (HPS)which strategy to improve hypoxemia should be recommended
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with chronic liver failure and hepatopulmonary syndrome (HPS) | Use of oxygen therapy to improve hypoxemia | Use of therapies other than oxygen (e.g. methylene blue, garlic etc.) to improve hypoxemia | MortalityOxygen saturationEligibility for liver transplantation |
| 1. In critically ill patients with chronic liver failure and hepatic hydrothorax should we perform tube thoracotomy
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with chronic liver failure and hepatic hydrothorax | Performing tube thoracotomy | Not performing tube thoracotomy | MortalityInfectionVolume and electrolyte loss |
| 1. In critically ill patients with ALF or ACLF who are hypoxic should we use high flow nasal cannula versus non-invasive positive pressure ventilation
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure who are hypoxic | High flow high humidity nasal cannula | Non-invasive positive pressure ventilation | MortalityRates of intubation Oxygen saturation |
| **RENAL** |
| 1. In critically ill patients with ALF or ACLF undergoing liver transplant surgery and receiving pre-operative renal replacement therapy (RRT) should we use intraoperative RRT
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure undergoing liver transplant surgery and receiving pre-operative RRT | Intra-operative RRT | No intra-operative RRT | MortalityGraft dysfunction |
| 1. In critically ill patients with ALF or ACLF who develop acute kidney injury (AKI) should we use early RRT versus late RRT
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with acute liver failure who develop AKI | Early RRT | Late RRT | MortalitySurvival to liver transplant |
| 1. In critically ill patients with chronic liver failure who develop hepatorenal syndrome (HRS) should we use vasopressors
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with chronic liver failure who develop HRS | Vasopressor | No intervention | MortalityRenal function |
| 1. In critically ill patients with chronic liver failure and refractory ascites should we use TIPS to prevent HRS
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with chronic liver failure and refractory ascites | TIPS | No intervention | MortalityDevelopment of HRSDevelopment of hepatic encephalopathy |
| **ENDOCRINE/NUTRITION/PHARMCACY** |
| 1. In critically ill patients with ALF or ACLF and hyperglycemia, should we target very tight (80 to 109 mg/dL) or conventional (110-180 mg/dL) glycemic control
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure and hyperglycemia | Very tight glucose control | Conventional glucose control | MortalityHypoglycemia |
| 1. In critically ill patients with ALF or ACLF and refractory septic shock, should we use stress-dose steroids (i.e. hydrocortisone 200 mg/day)
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure and refractory septic shock | Stress dose steroids | No intervention | MortalityReversal of shockOrgan failureHyperglycemiaNeuromuscular weakness |
| 1. In critically ill patients with ALF or ACLF, should be recommend a high protein (1.2 – 2.0 g/kg/day) diet as compared to a low protein (< 1.0 g/kg/day) diet?
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure | High protein diet | Low protein diet | MortalityHepatic Encephalopathy |
| 1. In critically ill patients hospitalized with ALF or ACLF who are receiving enteral or parenteral nutrition, should we recommend a formula high in branched-chain amino acids (BCAA) compared to a standard amino acid profile
 |
| Population  | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure | Nutrition formula high in branch chain amino acids | Nutrition formula with standard amino acid profile | MortalityHepatic Encephalopathy |
| 1. In critically ill patients with ALF or ACLF should we use enteral nutrition or parenteral nutrition
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure | Enteral Nutrition |  Parenteral nutrition | MortalityInfectious complicationsGastro-intestinal intolerance |
| 1. In critically ill patients with ALF or ACLF should we screen for drug induced causes of liver failure
 |
| Population | Intervention | Comparator | Outcomes(s) |
| Critically ill patients with liver failure | Screening for drug induced causes of liver failure | Not screening for drug induced causes of liver failure | MortalityTransplant free survival |
| 1. In critically ill patients with ALF or ACLF should we adjust doses of medications based on hepatic function
 |
| Population | Intervention | Comparator | Outcome(s) |
| Critically ill patients with liver failure | Dose adjustment of medications based on hepatic function | Not adjusting doses of medications based on hepatic function | MortalityDrug toxicity |