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Title: Recent Advances in the treatment of decompensated cirrhosis and acuteon-chronic liver failure (ACLF)

SUPPLEMENTARY MATERIAL

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SUPPLEMENTARY TABLE 1: Standard therapies

| Complication of cirrhosis | | Non-acute decompensation | Acute decompensation | ACLF |
|---------------------------------|-----------------------|---|--|--|
| Hepatic encephalopathy | | lactulose rifaximin BCAA, nutritional intervention | lactulose i.v. LOLA rifaximin+ BCAA+ nutritional intervention+ | lactulose i.v. LOLA ALS (e.g MARS) |
| GI-bleeding | | NSBB (prophylaxis) endoscopy (EVL) vasoconstrictors TIPS | endoscopy (EVL) vasoconstrictors TIPS | endoscopy (EVL) vasoconstrictors TIPS |
| Tense Ascites | Responsive ascites | nutritional intervention diuretics, | nutritional intervention* diuretics*, | nutritional intervention* albumin |
| | Recidivant ascites | diuretics TIPS albumin for LVP long-term albumin | TIPS albumin for LVP long-term albumin ⁺ | TIPS albumin long-term albumin ⁺ |
| | Refractory ascites | TIPS albumin for LVP long-term albumin | TIPS albumin for LVP long-term albumin⁺ | TIPS albumin RRT |
| SBP | | cephalosporins albumin (d1/d3) norfloxacin⁺ | cephalosporins albumin (d1/d3) norfloxacin (prophylaxis) ⁺ | broad-band antibiotics albumin (d1 and d3) norfloxacin (prophylaxis) ⁺ |
| Non-SBP infection | | antibiotics according to site of infection | antibiotics according to site of infection | antibiotics according to site of infection albumin |
| Alco | hol-related hepatitis | steroids [#] | steroids [#] | steroids [#] |
| Reactivation of viral hepatitis | | tenofovir | tenofovir | tenofovir (steroids) |
| АКІ | | stop nephrotoxic drugs albumin for 48h | stop nephrotoxic drugs albumin for 48h | stop nephrotoxic drugs albumin for 48h |
| HRS | | albumin terlipressin | albumin terlipressin | albumin terlipressin (except for ACLF III) |

* effect is expected in long-term; ⁺ at discharge; [#] according to Maddrey DF (Biggins et al. Hepatology. 2021 Aug;74(2):1014-1048; de Franchis et al. J Hepatol. 2022 Apr;76(4):959-974; EASL. J Hepatol. 2018 Aug;69(2):406-460; EASL. J Hepatol. 2023 Aug;79(2):461-491)

<u>Abbreviations</u>: AKI: acute kidney injury, HRS: hepatorenal syndrome, TIPS: transjugular portosystemic shunt; EVL: endoscopic variceal ligation; LVP: large volume paracentesis: d: day; ACLF: acute-on-chronic liver failure SBP: spontaneous bacterial peritonisis; GI: gastrointestinal: BCAA: Branched-chain amino acids; LOLA: I-Ornithine I-Aspartate; ALS: artificial liver support: MARS: Molecular adsorbent recirculating system; NSBB: non-selective beta blockers

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SUPPLEMENTARY TABLE 2. Example biomarker

| | Description | Examples | |
|--------------------------------------|---|---|--|
| Biomarker name | Specific analyte (e.g., fibronogen), anatomic feature (e.g., resistive index), physiological characteristic (e.g., hepatic pressure gradient) | Neutrophil gelatinase- associated lipocalin | Alanine aminotransferase |
| Acronym | | NGAL | ALT |
| Unique identifier (if applicable) | Formal chemical name or, if listed in a library or other resource, the correct name or unique identifier, referencing the resource and version. E.g. UniProt (<u>http://uniprot.org/</u>) HUGO Gene Nomenclature Committee (<u>http://genenames.org</u>), Protein Data Bank (<u>http://rcsb.org/pdb/home/home.do</u>), or Enzyme Commission (<u>http://enzyme.expasy.org</u>) | P80188 | EC 2.6.1.2 |
| Source | urine, biopsy, imaging, functional studies | Urinary | Serum |
| Туре | molecular, histologic, radiographic, digital, or physiologic | Molecular | Molecular |
| Biological plausibility | Brief summary of the biological, physiological, or pathological pathway for the association of the biomarker with ACLF and its intended use. This information specifies how multiple biomarkers may interplay as part of a common use (e.g., shared biochemical pathways leading to a common biologic or clinical phenotype) | Neutrophil gelatinase- associated lipocalin (NGAL)is upregulated in experimental models of liver injury and cultured hepatocytes as a result of injury by toxins or proinflammatory cytokines, particularly interleukin-6. Ariza et al. found that NGAL was a marker of ACLF and prognosis correlating with liver failure, systemic inflammation and overexpression of LCN2 gene in ACLF. J Hepatol. 2016 Jul;65(1):57-65 | ALT catalyses the transfer of an amino group from L-alanine to α-ketoglutarate, the products of this reversible transamination reaction being pyruvate and L- glutamate. In liver damage, it is released from hepatocyte injury into the circulation. |
| method | measure the biomarker to enable comparison across studies, e.g., ELISA | LIOA | detection |
| Units of measurement | | Mcg/gm creatinine | International Units/L |
| Point of care access/use? | | No | Yes |

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Supplementary Figure 1. . Drug discovery and development processes with a potential to benefit from biomarkers in different clinical phases

or regulatory approval (e.g., safety/monitoring)

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Supplementary Figure 2. The suggested biomarker validation approach. Draft guidance. Food and Drug Administration in 2018. Available at:

https://www.fda.gov/media/119271/download .



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Supplementary Figure 3. The evidentiary framework was drafted by the Food and Drug Administration when determining the type and level of

evidence sufficient to support the qualification of a biomarker. Available at: https://www.fda.gov/media/119271/download

