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EDITORIAL

The persistent potential of extracorporeal therapies in liver failure

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Alshamsi and co-authors performed a systematic review and meta-analysis of randomized controlled trials (RCT) to examine the efficacy and safety of extracorporeal liver support (ECLS) in patients with liver failure [1]. ECLS can be divided into artificial (cell-free systems) and bioartificial liver support devices that incorporate hepatocytes in an artificial device. The authors identified 25 RCTs including 1796 patients, and used the GRADE approach to assess the certainty of evidence. Thirteen RCTs assessed patients with acute liver failure (ALF) and 13 RCTs investigated patients with acute-on-chronic liver failure (ACLF). Nineteen trials used artificial ECLS and five trials used bio-artificial ECLS. The authors observed a significant association of ECLS and reduction in mortality (RR 0.84, 95% CI 0.74–0.96, moderate certainty) and significant improvement in hepatic encephalopathy (RR 0.71, 95% CI 0.60–0.84, low certainty) in patients with ALF and ACLF. Subgroup analysis did not observe a difference of outcome using ECLS in patients with ALF and ACLF. Furthermore, kind of device, risk of bias and funding source did not reveal significant subgroup differences. Additional sensitivity analysis excluding four studies published in abstract form revealed similar results. The number needed to treat was 22 in patients with ALF and 16 in patients with ACLF. In summary, this systematic review and meta-analysis provides evidence that ECLS may reduce mortality in patients with ALF and ACLF. This effect was more prominent with artificial than with bio-artificial devices.

Liver failure in critical illness

Over the last decades the incidence of liver injury and failure in critically ill patients has increased significantly. A recent European multinational analysis reported an increase from 5 to 20% of all patients treated at the intensive care unit (ICU) [2]. Liver failure is a classical form of multi organ failure as already represented in the diagnostic criteria of its different entities: ALF is defined as defined as onset of hepatic encephalopathy and hepatic coagulopathy (INR > 1.5) in patients without underlying liver disease [3, 4]; ACLF is defined as presence of acute hepatic decompensation (i.e. ascites, hepatic encephalopathy, gastrointestinal bleeding or bacterial infection in patients with chronic liver disease) in combination with (mainly extrahepatic multi-)organ failure [5, 6]. In critical illness all types of liver failure increase morbidity and mortality dramatically [4]. Therapy should focus on prompt removal of the underlying trigger causing the hepatic injury like treatment of cardiac failure, sepsis or gastrointestinal bleeding. The main therapeutic aim is focused on avoidance of progression of multiorgan failure mainly by symptomatic multimodal treatment with bundles of care [3–5] (Fig. 1).

Extracorporeal therapies in liver failure

Extracorporeal therapies form a cornerstone of treatment in all different kinds of liver failure; 60–70% of patients with liver failure suffer from acute kidney injury and 30–40% require extracorporeal therapies [7–9]. Although renal replacement therapies (RRT) are most commonly used in patients with liver failure during daily clinical practice, randomized controlled trials have only been performed with ECLS devices, not with RRT. While several artificial ECLS (such as MARS©, Prometheus©,

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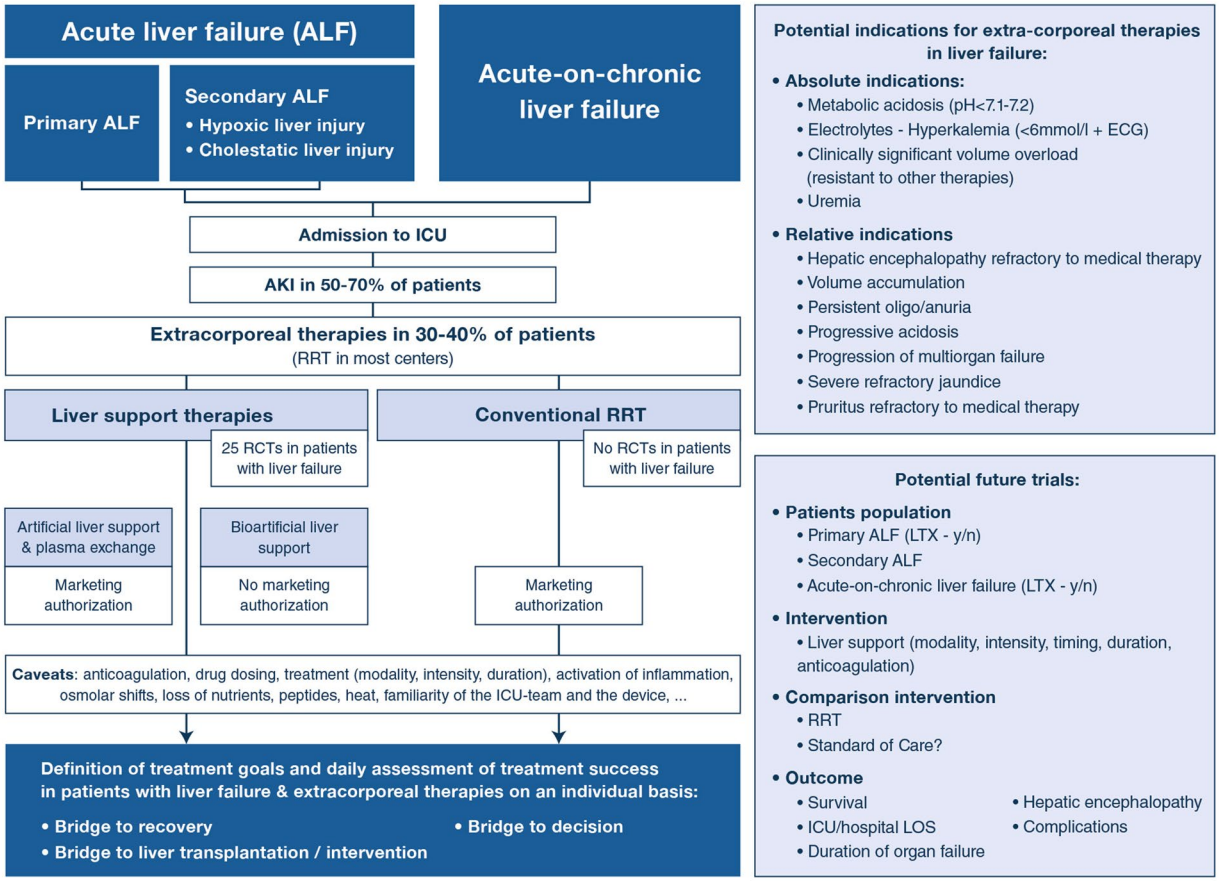

Fig. 1 Overview of types of liver failure and extracorporeal therapies. Incidence of liver injury and failure is increasing in critically ill patients. Most frequently, patients suffer from secondary forms of acute liver failure (hypoxic liver injury and cholestatic liver failure, observed in 5–20% of critically ill patients) followed by acute on chronic liver failure (observed in 2–5% of the ICU-population) and primary acute liver failure (< 10 cases per million persons/year) [4, 5]. Definition of treatment goals and repeated evaluation of the patients are of central importance in management of patients with liver failure that receive ECLS. *ALF* acute liver failure, *RRT* renal replacement therapies, *AKI* acute kidney injury, *LTX* liver transplantation, *y/n* yes/no, *ECG* electrocardiogram, *ICU* intensive care unit, *LOS* length of stay, *RCT* randomized controlled trial, *ECLS* extracorporeal liver support

ADVOS©, etc.) have marketing authorization in many countries all over the world, bio-artificial devices are only used in clinical trials. Although artificial ECLS may represent a distinct entity of extracorporeal devices as a kind of modular assembly systems, they can be regarded as "advanced dialysis" devices: in addition to the properties of conventional RRT they are able to eliminate albumin bound substances and may have additional abilities [10]. Artificial ECLS is usually used as bridge to recovery or to liver transplantation in patients with different kinds of liver failure [11].

Current analysis in context of available literature

What does this systematic review and meta-analysis of randomized controlled trials (RCT) add to the available literature? In accordance with other recent meta-analyses, the present data provide further evidence that ECLS may improve survival in patients with liver failure [12–14]. Compared to the most recent previous analyses, this study was able to incorporate data from more studies.

However, several uncertainties in the use of ECLS in patients with liver failure remain. First, there is a lack of RCTs assessing the effect of the extracorporeal device that is most frequently used during daily clinical practice in patients with liver failure: conventional RRT. Therefore, this treatment modality could not be incorporated in the current analysis by Alshamsi et al. Furthermore, up to date there is no RCT comparing kinds of ECLS to conventional RRT or other ECLS devices in patients with liver failure. Third, the currently most cited and accepted definition of ACLF (definition by the CLIF-consortium)

was established in 2013 [6]. Many of the cited RCTs were designed and performed prior to the established ACLF-definition, so the term ACLF must be considered with caution in this analysis. Furthermore, central issues of clinical practice like (a) when to start, (b) which treatment modality should be preferred, (c) intensity and (d) duration of extracorporeal therapy have to be clarified by future trials. In this regard, a recent meta-analysis of pooled individual-patient data of albumin dialysis in patients with ACLF showed that high treatment intensity (>4 albumin dialysis sessions) was associated with significantly higher survival rates in patients with ACLF [14].

In conclusion, extracorporeal therapies remain of fundamental interest in the management of liver failure and the initial management of multiorgan failure as bridging device [15]. This systematic review and meta-analysis provides further evidence that ECLS may improve survival in patients with ACLF and ALF. Future RCTs are warranted to specify timing, treatment modalities and duration and to compare clinical impact of different ECLS devices and conventional RRT.

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Compliance with ethical standards

Conflicts of interest
V Fuhrmann made lectures by CLS-Behring, Merz, Gambro, Fresenius, ADVITOS. M Bauer made lectures by ADVITOS. A Wilmer has nothing to declare.

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