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SYSTEMATIC REVIEW

Extracorporeal liver support in patients with liver failure: a systematic review and meta-analysis of randomized trials

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Abstract

Purpose: Acute liver failure (ALF) and acute on chronic liver failure (ACLF) are associated with significant mortality and morbidity. Extracorporeal liver support (ECLS) devices have been used as a bridge to liver transplant; however, the efficacy and safety of ECLS are unclear. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to examine the efficacy and safety of ECLS in liver failure.

Methods: We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials from inception through March 13, 2019. RCTs comparing ECLS to usual care in ALF or ACLF were included. We used the Grading of Recommendations Assessment, Development and Evaluation approach to assess the certainty of the evidence.

Results: We identified 25 RCTs (1796 patients). ECLS use was associated with reduction in mortality (RR 0.84; 95% CI 0.74, 0.96, moderate certainty) and improvement in hepatic encephalopathy (HE) (RR 0.71; 95% CI 0.60, 0.84, low certainty) in patients with ALF or ACLF. The effect of ECLS on hypotension (RR 1.46; 95% CI 0.98, 2.2, low certainty), bleeding (RR 1.21; 95% CI 0.88, 1.66, moderate certainty), thrombocytopenia (RR 1.62; 95% CI 1.0, 2.64, very low certainty) and line infection (RR 1.92; 95% CI 0.11, 33.44, low certainty) was uncertain.

Conclusions: ECLS may reduce mortality and improve HE in patients with ALF and ACLF. The effect on other outcomes is uncertain. However, the evidence is limited by risk of bias and imprecision, and larger trials are needed to better determine the effect of ECLS on patient-important outcomes.

Keywords: Extracorporeal liver support, Acute liver failure, Acute on chronic liver failure, Albumin dialysis, Hemoperfusion, Exchange transfusion

Introduction

Liver failure may occur with or without underlying liver disease. Acute liver failure (ALF) occurs without underlying chronic liver disease, and usually causes jaundice, coagulopathy, encephalopathy, and can progress to multi-organ failure and death [1, 2]. While some patients recover with supportive care, the definitive treatment for those who do not recover is liver transplantation, which

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is expensive and limited by the availability of organs. Extracorporeal liver support (ECLS) offers a potential option for bridging to transplantation or allowing longer time for recovery [3]. The concept behind the use of ECLS is to remove the hepatotoxic substances such as cytokines, vasoactive substances, endotoxins from gut flora, and low molecular weight toxins [2]. However, the contradicting results from previous literature have limited its use [3–11]. Although it can be used as a bridging therapy to transplant, it is unclear if ECLS improves survival among patients with ALF who are not candidates for liver transplantation.

ECLS systems are based on dialysis techniques to remove toxic substances such as nitric oxide, prostaglandins, reactive oxygen species, and pathogen-associated molecular patterns that may play a role in liver failure pathogenesis. Artificial systems use cell-free techniques for plasma filtration either by dialysis or exposure to an exchange medium such as charcoal [12]. Commonly used artificial systems include Molecular Adsorbent Recirculating System (MARS, Gambro, Lund, Sweden) and fractionated plasma separation and adsorption (SEPAD; Prometheus, Fresenius Medical Care GmbH, Bad Homburg, Germany), hemofiltration and plasma exchange [12]. On the other hand, bio-artificial systems use either human-based liver cells (e.g., ELAD, Vital Therapies Inc., San Diego, California, USA) or porcine liver cells (e.g., HepatAssist, Arbios, formerly Circe, Waltham, Massachusetts, USA). Besides detoxification of aforementioned substances, bio-artificial systems may have an additional benefit by supporting metabolic and synthetic liver function [13]. However, none of these modalities is designed to assist in the other major liver function of immune modulation [14].

ALF is defined as hepatic encephalopathy (HE) that occurs within 8–28 days from the onset of jaundice, with a high incidence of cerebral edema and a poor prognosis without liver transplantation [15]. Acute on chronic liver failure (ACLF), is distinct from ALF in which patients have pre-existing chronic liver diseases. The Asian Pacific Association for the Study of the Liver defines ACLF as "an acute hepatic insult manifesting as jaundice (serum bilirubin $\geq$ 5 mg/dl (85 micromol/l) and coagulopathy (INR $\geq$ 1.5 or prothrombin activity < 40%) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis" [16]. The European Association for the Study of the Liver and the American Association for the Study of Liver Diseases define ACLF as "acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure" [17].

Several factors can affect the prognosis of patients with ALF or ACLF. For those listed for liver transplantation, the mortality rate is 29% for patients with ALF, and up to 48% for patients with ACLF [18]. In the North American Consortium for the Study of End-stage Liver Disease (NASCELD) study, the mortality was 40% in ACLF patients, and was as high as 77% in those with additional organ failures [19, 20]. The clinical course of ACLF is variable, spontaneous resolution can be as high as 50% in the absence of organ failure, and only 15% in patients with multi-organ failure [21].

Take-home message

The use of extracorporeal liver support devices in patients with ALF and ACLF may improve mortality and hepatic encephalopathy. Future studies are needed to confirm these results and to determine which modality is most effective.

The impact of ECLS on clinical outcomes of patients with ALF or ACLF is unclear. Therefore, we conducted a systematic review and meta-analysis of randomized trials to determine the efficacy and safety of artificial or bio-artificial ECLS modalities in patients with liver failure [22].

Methods

Study protocol

We registered the study protocol with the International Prospective Register of Systematic Reviews (PROSPERO; ID CRD42018080201). We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [23].

Study selection

Eligible studies met the following criteria: (1) the study design was a randomized controlled trial (RCT); (2) the population were adults with ALF or ACLF; (3) the interventions were any form of artificial or bio-artificial ECLS; (4) the control group received supportive care not including ECLS; (5) the outcomes were all-cause mortality or liver-related mortality, bridging to liver transplant, improvement of HE and adverse events such as hypotension, bleeding, thrombocytopenia, line infection, and citrate toxicity. All outcomes were assessed at the longest follow-up reported in the studies.

Search strategy and data extraction

We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from inception through March 13, 2019 [Electronic Supplemental Material (ESM) Tables 1, 2)]. We assessed citations for eligibility without language, date or type of publication restrictions. In addition, we screened references of relevant articles to identify additional citations. Two reviewers (FA and EB) independently and in duplicate screened titles and abstracts

for full-text review and evaluated the full-text articles for eligibility. Two reviewers (FA and BA) also, independently and in duplicate, extracted relevant data from eligible studies using a standardized form. We attempted to contact study authors to obtain missing data. Disagreements were resolved through discussion or a third arbitrator.

Risk of bias assessment

Two reviewers (JD and KA), independently and in duplicate, assessed the risk of bias of individual trials using the Cochrane Collaboration Risk of Bias tool [24]. Reviewers judged trials to be at low, unclear or high risk of bias for each domain. Reviewers deemed the overall risk of bias for individual trials low if all domains were at low risk, unclear if at least one domain was unclear, but no domain was at high risk of bias, and high risk if any domain was at high risk of bias.

Statistical analysis

We used RevMan software (Review Manager, version 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) for data analysis. We used the DerSimonian and Laird random-effects model to pool the weighted estimates across studies [25] and the inverse variance method to estimate study weights. For dichotomous outcomes, we report pooled relative risk (RR) with corresponding 95% confidence interval (CI). We defined significant statistical heterogeneity using Chi^2 $P < 0.10$ or $I^2 > 50\%$ [26].

We used the Cochrane Collaboration method to calculate the number needed to treat (NNT) [27]. Based on recent observational studies, we used an assumed control risk (ACR) of 25% and 40% for mortality in ALF and ACLF, respectively [19, 20, 28]. For outcomes with over ten studies we inspected funnel plots visually to assess for publication bias and used Egger's test to assess for publication bias [29].

We performed predetermined subgroup analyses to explore whether specific factors influenced treatment effects. Pre-specified subgroup analyses were artificial versus bio-artificial treatment modalities and low versus high and unclear risk of bias studies. In addition, post hoc subgroup analyses by type of liver failure (ALF versus ACLF) and funding source were performed. We performed a post hoc sensitivity analysis excluding trials published as abstracts only. For subgroup analyses, we tested for interaction using a χ^2 significance test [30].

Finally, we performed a post hoc trial sequential analysis (TSA) to explore the risk of random errors in cumulative meta-analyses [31–34]. Trial sequential monitoring boundaries adjust the Z score (P value) for significance each time a trial is added to the meta-analysis (i.e., accounting for multiple testing and accrued information). We considered a cumulative Z curve that is greater than the trial sequential boundary a significant effect. Thus, if cumulative Z curve crossed trial sequential significance boundary, we inferred that the intervention is superior to control, even if sample size did not reach required meta-analysis sample size. We aimed to maintain an overall 5% risk of a type I error and a power of 80%. For the required information size (RIS) calculations we used a relative risk reduction (RRR) of 20%, and user-defined incidence rates estimated from all included trials in the conventional meta-analyses for mortality (45.95%) and HE (45.6%) outcomes.

Assessment of quality of evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to classify the certainty of evidence into high, moderate, low, or very low for each outcome [35]. Well-conducted RCTs provide high certainty but can be downgraded based on the following five domains: risk of bias, inconsistency, indirectness, imprecision and reporting bias.

Results

Our search identified 1068 records. After removing duplicates, 944 records remained. Of those, we excluded 873 irrelevant records. We assessed the remaining 71 full-text articles and further excluded 46 articles. We included 25 studies (enrolling 1796 patients) that met our eligibility criteria (ESM Fig. S1) [36–60].

Thirteen RCTs enrolled patients with ALF [37–39, 41–43, 45, 48, 52, 53, 56, 57, 59] and 13 RCTs enrolled patients with ACLF [36, 40, 44–47, 49, 50, 54, 55, 58–60]. The average age across all studies was 44 years, and males constituted 59% of all patients. The most common etiologies for ALF were alcohol, viral hepatitis and acetaminophen toxicity. Nineteen trials used artificial ECLS [36–38, 41, 42, 44–46, 48–50, 52–59] and only five trials used bio-artificial ECLS [39, 40, 43, 47, 60]. Trials were mainly from USA, Europe, and Asia. Among artificial systems, MARS (Teraklin AG, Rostock, Germany) [36, 41, 44, 46, 51, 54, 57, 58] was the most commonly used followed by Biologic-DT (HemoCleanse, Inc., West Lafayette, IN, USA) [42, 48, 49, 53, 59], FPSA (Prometheus, Fresenius Medical Care Deutschland GmbH 61346 Bad Homburg v. d. H. Germany) [50, 51], plasma exchange with hemoperfusion [45], whole blood exchange [56] and charcoal hemoperfusion [37]. Bio-artificial modalities included extracorporeal liver assist device (ELAD, Vital Therapies Inc., San Diego, CA, USA) [40, 47, 60] and HepatAssist (Circe Biomedical Inc., Lexington, MA, USA) [39]. Funding was from a combination of academia and industry in 16 trials [36–38, 41, 43, 45, 46, 49, 51–58] and from industrial sources in 9 trials [39, 40, 42, 44, 47,

Table 1 Characteristics of included studies

Study	Population	Interventions	Control	Outcomes	Funding
Redeker [56] 1973 USA	ALF with Grade IV hepatic encephalopathy	Exchange transfusion: $n=15$ Etiology: 1. Viral: 100% Age (mean): 25 Male: 60%	Standard medical therapy: $n=13$ Etiology: 1. Viral: 100% Age (mean): 23 Male: 53%	Mortality[a]	Academic
O'Grady [37] 1988 UK	ALF with Grade IV hepatic encephalopathy[b] 1. Acetaminophen: 51.6% 2. Viral: 40.4% 3. Halothane/drug reactions: 8%	Hemoperfusion: $n=29$ 10 h/day Median 2 sessions	Standard medical therapy: $n=33$	Mortality[a]	Academic
Hughes [48] 1994 UK	ALF with Grade IV hepatic encephalopathy	BioLogic-DT: $n=5$ 6 h/day until any of: 1. 5 days total 2. Death 3. Recovery Etiology: 1. Acetaminophen: 40% 2. Hepatitis: 60% Age (mean): 42 Male: 60%	Standard medical therapy: $n=5$ Etiology: 1. Acetaminophen: 80% 2. Hepatitis: 20% Age (mean): 33 Male: 80%	Mortality[a] Hepatic encephalopathy Adverse events	Possible industry[c]
Ellis [43] 1996 UK	ALF	ELAD: $n=12$ *N*-Acetylcysteine (150 mg/kg over 24 h) Median duration: 62 h Criteria for stopping: 1. INR ≤ 2 2. Liver transplant available 3. Irreversible hypotension with vasopressors Etiology: 1. Acetaminophen: 71% 2. Viral: 21% 3. Drug reactions: 8% Age (median): 30 years Male: 50%	Standard medical therapy: $n=12$ *N*-acetylcysteine (150 mg/kg over 24 h) Etiology: 1. Acetaminophen: 71% 2. Viral: 21% 3. Drug reactions: 8% Age (median): 30 years Male 50%	Mortality[a] Hepatic encephalopathy Adverse events	Not clear
Mazariegos [53] 1997 USA Abstract	ALF with coma[d]	BioLogic-DT: $n=5$ 6 h/day for 3 days	Standard medical therapy: $n=1$	Mortality[a] Hepatic encephalopathy	Academic and industry[e]
Wilkinson [59] 1998 USA	ALF with Grade III–IV hepatic encephalopathy	BioLogic-DT: $n=6$ 6 h/day for up to 5 days Criteria for stopping: 1. Liver transplant 2. Rejection of liver transplant 3. Death 4. Recovery of liver function and consciousness Etiology: 1. Viral: 50% 2. Alcoholic: 33% 3. Chronic autoimmune hepatitis: 17% Age (mean): 58 years Male: 67%	Standard medical therapy: $n=5$ Etiology: 1. Viral: 20% 2. Alcoholic: 20% 3. Cryptogenic cirrhosis: 20% 4. Hemochromatosis: 20% Heat shock: 20% Age (mean): 40 years Male: 80%	Mortality[a] Hepatic encephalopathy Adverse events	Possible industry[f]
Ellis [42] 1999 UK	ALF and Grade II or higher hepatic encephalopathy	BioLogic-DT: $n=5$ 6 h/day for 3 days Etiology: 1. Alcoholic: 100% Age (median): 46 years Male: 60%	Standard medical therapy: $n=5$ Etiology: 1. Alcoholic: 100% Age (median): 43 years Male: 80%	Mortality: in-hospital Adverse events	Industry[g]

Table 1 (continued)

Study	Population	Interventions	Control	Outcomes	Funding
He [45] 2000 China	ALF: hepatitis (100%) ACLF: hepatitis (100%) Age (mean): 38 years Male 87%	Plasma exchange/perfusion and hemoperfusion: $n=37$ $n=27$ Mean 2.6 treatments	Standard medical therapy: $n=33$ $n=27$	Mortality: in-hospital Hepatic encephalopathy Adverse events	Not clear
Mitzner [54] 2000 Germany	ACLF: hepatorenal syndrome or acute deterioration of CLD	MARS ± hemodiafiltration (HDF): $n=8$ 6 h/day up to 10 days Etiology: 1. Alcoholic: 62.5% 2. Viral: 25% 3. Primary biliary cirrhosis 12.5% 4. Secondary biliary cirrhosis: 8% Age (mean): 50 years Male: 38%	Standard medical therapy + HDF: $n=5$ Etiology: 1. Alcoholic: 40% 2. Viral: 40% 3. Secondary biliary cirrhosis: 20% Age (mean): 44 years Male: 40%	Mortality: 30-days Adverse events	Academic and industry[h]
Kramer [49] 2001 Austria	ACLF and hepatic encephalopathy	BioLogic-DT: $n=10$ 6 h/treatment Etiology:[i] 1. Alcoholic: 60% 2. Viral 3. Autoimmune hepatitis 4. Cryptogenic Age (median): 56 years Male: 65%[j]	Standard medical therapy: $n=10$ Etiology:[i] 1. Alcoholic: 70% 2. Viral 3. Autoimmune hepatitis 4. Cryptogenic Age (median): 55 years Male: 65%[j]	Mortality: ICU and 30-days Hepatic encephalopathy Adverse events	Academic and industry[k]
Heeman [46] 2002 Germany	ACLF	MARS: $n=12$ Maximum 10 treatments Etiology of CLD:[l] 1. Alcoholic: 83% 2. Viral: 17% Acute failure etiology:[m] 1. Alcoholic: 70% 2. Infection: 50% 3. Bleeding: 25% 4. Drugs 17% 5. Viral: 8% Age (mean): 48 years Male: 50%	Standard medical therapy: $n=12$ Etiology of CLD: 1. Alcoholic: 82% 2. Drugs: 17% 3. Primary biliary cirrhosis: 10% Acute failure etiology:[m] 1. Infection: 33% 2. Alcoholic: 75% 3. Drugs 17% 4. Bleeding: 8% Age (mean): 53 years Male: 37%	Mortality: 30-days Hepatic encephalopathy Adverse events	Academic and industry[n]
Demetriou [39] 2004 USA and Europe	ALF: $n=147$ PNF:[o] $n=24$	HepatAssist: $n=85$ 6 h/day up to 14 days Criteria for stopping: 1. Liver transplant 2. Clinical improvement 3. Deterioration 4. Adverse events 5. Death Etiology: 1. Viral, acetaminophen and other toxins: 47% 2. Unknown: 39% 3. PNF: 14% Age (mean): 37.2 years Male: 29%	Standard medical therapy: $n=86$ Etiology: 1. Viral, Acetaminophen and other toxins: 50% 2. Unknown: 36% 3. PNF: 14% Age (mean): 37 years Male: 30%	Mortality: 30-days randomization Adverse Events	Industry[p]
El Banayosy [41] Abstract 2004 USA	ALF due to cardiogenic shock after cardiac surgery[q]	MARS: $n=14$ 3 consecutive days	Standard medical therapy: $n=13$	Mortality[a]	Not clear

Table 1 (continued)

Study	Population	Interventions	Control	Outcomes	Funding
Sen [58] 2004 UK	ACLF	MARS: $n=9$ 8 h sessions 4 times in 7 days Etiology of CLD: 1. Alcoholic: 67% 2. Alcoholic + HCV:[r] 33% Acute failure due to: 1. Alcoholic: 56% 2. Infection: 44% Age (mean): 45 years Male: 78% Child–Turcotte–Pugh class C: 100%	Standard medical therapy: $n=9$ Etiology of CLD: 1. Alcoholic: 100% Acute failure due to: 1. Infection: 67% 2. Alcoholic: 33% Age (mean): 44 years Male: 67% Child–Turcotte–Pugh class C: 100%	Mortality: in-hospital Hepatic Encephalopathy	Academic and industry[s]
Laleman [51] 2006 Belgium	ACLF: alcoholic 100% MELD score (mean): 26 Age (mean): 51 years Male: 67%	MARS: $n=6$ 6 h/day for 3 days MELD score (mean): 22.7 Age (mean): 55 years Male: 83% Prometheus: $n=6$ 6 h/day for 3 days MELD score (mean): 29.7 Age (mean): 43 years Male: 67%	Standard medical therapy: $n=6$ MELD score (mean): 24.3 Age (mean): 56 years Male: 50%	Adverse events	Academic and industry[t]
Duan [40] 2007 China Abstract	ACLF: chronic HBV[u] or HCV with acute decompensation	ELAD: $n=35$ Continuous until recovery (mean: 72 h) Etiology of CLD: 1. HBV: 67% 2. HCV: 33% MELD score (mean): 28.4 Age (mean): 40 years Male: NA	Standard medical therapy: $n=19$ Etiology of CLD: 1. HBV: 67% 2. HCV: 33% MELD score (mean): 31 Age (mean): 40 years Male: NA	Mortality: 30-days Adverse events	Possible industry[v]
Hassanein [44] 2007 USA and Germany	ACLF: cirrhosis with hepatic encephalopathy Grade III or IV	MARS: $n=39$ 6 h/day until: 1. 5 treatments 2. Improvement of hepatic encephalopathy by 2 grades 3. Liver transplant 4. Withdrawal of consent 5. Death Etiology of CLD: 1. Alcoholic: 39% 2. Viral (HBV/HCV): 28% 3. Alcoholic + viral: 15% 4. Cryptogenic: 10% 5. AIH/PSC:[w] 7% Acute failure etiology: 1. Infection: 26% 2. Bleeding: 15% 3. Electrolyte imbalance: 8% 4. Other: 18% 5.Unknown 33% Age (median): 49 years Male: 62% MELD score (median): 33 Child–Turcotte–Pugh score (median): 13	Standard medical therapy: $n=31$ Etiology of CLD: 1. Alcoholic: 39% 2. Viral (HBV/HCV): 32% 3. Alcoholic + viral: 10% 4. Cryptogenic: 6% 5. AIH/PSC:[w] 6% 6. Drugs: 3% Acute failure etiology: 1. Infection: 32% 2.Bleeding: 10% 3. Electrolyte imbalance: 19% 4. Other: 19% 5. Unknown 19% Age (median): 56 years Male: 48% MELD score (median): 28 Child–Turcotte–Pugh score (median): 12	Mortality: 5 days and 6 months Hepatic encephalopathy Adverse events	Industry[x]

Table 1 (continued)

Study	Population	Interventions	Control	Outcomes	Funding
Kribben [50] 2012 Europe	ACLF: mixed	Prometheus: $n=77$ 4 h/session Week 1: 5 sessions Week 2: 3 sessions Week 3: 3 sessions only if: 1. Bilirubin $\geq$ 5 mg/dL 2. Child–Pugh: no reduction of at least 2 points to less than 10 Etiology of CLD: 1. Alcoholic: 48% 2. Viral: 20% 3. Alcoholic + Viral: 10% 4. Other: 22% Acute failure etiology: 1. Infection: 46% 2. Alcoholic: 9% 3. Other/unknown: 45% Age (mean): 51 Male: 63% MELD score (median): 28 Child–Turcotte–Pugh score (median): 12	Standard medical therapy: $n=68$ Etiology of CLD: 1. Alcoholic: 65% 2. Viral: 21% 3. Alcoholic + Viral: 3% 4. Other: 12% Acute failure etiology: 1. Infection: 43% 2. Alcoholic: 10% 3. Other/unknown: 47% Age (mean): 51 Male: 63% MELD score (median): 28 Child–Turcotte–Pugh score (median): 12	Mortality: 28 and 90 days Adverse events	Industry[y]
Banares [36] 2013 Europe	ACLF: mixed	MARS: $n=90$ 8 h/session 4 sessions/day for 4 days then 3 sessions/week, maximum of 10 sessions or improvement defined as all of: 1. Creatinine < 1.5 mg/dL 2. HE grade < 1 3. stable bilirubin for 2 days without MARS and > 20% reduction from baseline Etiology of CLD: 1. Alcoholic: 81% 2. Other: 19% Etiology of ALF: 1. Alcoholic: 76% 2.Infection: 30% 3.SBP: 14% 4. GI Bleeding: 10% 5.Dehydration: 9% 6.Others: 4% Age (mean): 52 Male: 67% MELD score (mean): 25.6 Child–Turcotte–Pugh score (mean): 10.8	Standard medical therapy: $n=89$ Etiology of CLD: 1. Alcoholic: 83% 2. Other: 17% Etiology of ALF: 1. Alcoholic: 76% 2.Infection: 30% 3. SBP: 7% 4. GI Bleeding: 15% 5. Dehydration: 10% 6. Others: 6% Age (mean): 50 Male: 71% MELD score (mean): 24.1 Child–Turcotte–Pugh score (mean): 10.9	Mortality: 28-days Hepatic Encephalopathy Adverse events	Academic and industry[z]

Table 1 (continued)

Study	Population	Interventions	Control	Outcomes	Funding
Saliba [57] 2013 France	ALF	MARS: $n=53$ ≥ 5 h/session 5 sessions in 4 days then 2–3 sessions/week until either: 1. Transplant 2. Therapeutic response: a. prothrombin or factor V levels > 30% without plasma infusion b. and one of: (i) Hepatic encephalopathy grade ≤ 1 (ii) Reduction HE ≥ 2 stages (iii) Total bilirubin level less < 300 mol/L (17.5 mg/dL) Etiology: 1. Acetaminophen: 38% Viral: 15% 2. Autoimmune: 8% 3. Drug-induced: 6% 4. Mushroom poisoning: 9% 5. Toxic: 4% 6. Unknown: 9% 7. Other: 13.2% Age (mean): 40 years Male: 43% MELD score (mean): 37.6	Standard medical therapy: $n=49$ Etiology: 1.Acetaminophen: 39% 2.Viral: 12% 3.Autoimmune: 16% 4. Drug-induced: 14% 5.Mushroom poisoning: 6% 6. Toxic: 8% 7. Unknown: 6% 8. Other: 4% Age (mean): 41 years Male: 43% MELD score (mean): 38	Mortality: 6-months Adverse events	Academic[aa]
Qin [55] 2014 Singapore	ACLF	Plasma exchange ± hemoperfusion or hemodiafiltration: $n=104$ 3 treatments in 10 days then as needed Etiology: 1. HBV: 100% Age (mean): 44 years Male: 83% MELD score (mean): 28.56 Child–Turcotte–Pugh score (mean): 11.21	Standard medical therapy: $n=130$ Etiology: 1. HBV: 100% Age (mean): 49 years Male: 72% MELD score (mean): 29.46 Child–Turcotte–Pugh score (mean): 11.87	Mortality: 90-days Adverse events	Academic[ab]
Larsen [52] 2016 Europe	ALF	Plasma exchange: $n=92$ 15% of ideal body weight (8–12 L/day) patient plasma removed at 1–2 L/h and replaced with FFP 3 treatments over 3 consecutive days Etiology: 1. Acetaminophen: 50% 2.Unknown: 22% 3. Toxins: 11% 4. Viral: 6% 5. Other: 3% Age (mean): 46 Male: 28%	Standard medical therapy: $n=90$ Etiology: 1. Acetaminophen: 58% 2. Unknown: 17% 3. Toxins: 6% 4. Viral: 5% 5. Other: 2% 6. Budd-Chiari: 2% Age (mean): 45 Male: 37%	Mortality: in-hospital Adverse events	Academic[ac]
Hillebrand [47] 2010 USA Abstract	ACLF 1. SOFA ≥ 9 at screening and either: 2.MELD ≥ 32 or 3. MELD ≥ 24 and at least one of a. HE Grade III–IV b. HRS type 1	ELAD: $n=14$ MELD score (mean): 34.3	Standard medical therapy: $n=4$ MELD score (mean): 40.8	Mortality: 30 and 90-days	Possible industry[ad]

Table 1 (continued)

Study	Population	Interventions	Control	Outcomes	Funding
Thompson [60] 2018 USA	ACLF	ELAD: $n=96$ Continuously for 120 h Criteria for stopping any of: 1. subjects deteriorated and became futile 2. withdrawal of consent 3. responded quickly after 72 h Severe alcoholic hepatitis (sAH) MELD < 35 Heavy alcohol abuse with < 6 weeks from last intake and onset of jaundice and coagulopathy 1. sAH on liver biopsy or 2 of: 95% a. Hepatomegaly b. AST > ALT c. Leukocytosis d. Ascites 2. sAH and underlying chronic liver disease of other etiology confirmed on liver biopsy, laboratory findings or medical history: 4% (Randomized in different strata) Age (mean) 47 Males: 57% MELD (mean): 27.6	Standard medical therapy: $n=107$ Severe alcoholic hepatitis (sAH) MELD < 35 Heavy alcohol abuse with < 6 weeks from last intake and onset of jaundice and coagulopathy 1. sAH on liver biopsy or 2 of: 94% a. Hepatomegaly b. AST > ALT c. Leukocytosis d. Ascites 2. sAH and underlying chronic liver disease of other etiology confirmed on liver biopsy, laboratory findings or medical history: 6% (Randomized in different strata) Age (mean) 45 Males: 61% MELD (mean): 27.1	Mortality: 91-days Adverse events	Industry[ae]
Zhou [38] 2017 China	ALF	Plasma exchange: $n=22$ Average three sessions Etiology: 1. Paraquat: 32% 2. Drugs: 32% 3. Thinner: 18% 4. Fish gallbladder: 18% 5. Poisonous mushroom: 18% Age (mean): 46 years Male: 55%	Standard medical therapy: $n=21$ Etiology: 1. Paraquat: 33% 2. Drugs: 29% 3. Thinner: 10% 4. Fish gallbladder: 5% 5. Poisonous mushroom: 5% 6. Alcoholic: 5% 7. Organophosphates poisoning: 14% Age (mean): 46 years Male: 61%	Mortality: 6-months Hepatic encephalopathy	Academic

[a] Timeframe not reported

[b] Details of etiology per arm and demographics not reported

[c] Acknowledged Hemocleanse, Inc., West Lafayette, IN for supplying equipment

[d] Details on etiology and demographics of patient population not reported

[e] Partially supported by Hemocleanse, Inc., West Lafayette, IN

[f] One author's affiliation is Hemocleanse, Inc., West Lafayette, IN

[g] Acknowledged Hemocleanse, Inc., West Lafayette, IN. and Gambro Ltd. for providing us with the use of Biologic-DTsorbent suspension dialysis and consumables ad support for the cytokines assays

[h] Supported in part by a grant from the German Ministry for Research and Technology, Bonn; Gambro Dialysatoren GmbH & Co KG, Hechingen; and Teraklin AG, Rostock, Germany

[i] Percentages of etiologies other than alcoholic cirrhosis were not reported per arm

[j] Reported for the full cohort and not per arm (13 of 20)

[k] Supported government entity and in parts by Comesa Gesellschaft, Vienna, and HemoCleanse Inc

[l] CLD = chronic liver disease

[m] Multiple patients had more than one precipitating factor for acute liver failure, as such cumulative percentages will be more than 100%

[n] Supported in part by the German Ministry for Research and Development and Teraklin AG, Rostock, Germany

[o] PNF = primary nonfunction

[p] Sponsored by Circe Biomedical Inc

[q] Demographic details not reported

[r] HCV = hepatitis C virus

[s] Supported by the Sir Siegmund Warburg Voluntary Settlement. Teraklin AG, Germany, provided the MARS kits for the study, free of cost

Table 1 (continued)

[t] The authors state that the kits needed for the treatment of patients were offered by Teraklin Ltd (MARS) and by Fresenius Medical Care (Prometheus), respectively. Neither manufacturer funded the authors financially nor were they involved in the local study design with regard to these devices

[u] HBV = hepatitis B virus

[v] Study is listed as a publication on Vital Therapies Inc. website

[w] AIH = autoimmune hepatitis; PSC = primary sclerosing cholangitis

[x] Supported by grants from Teraklin AG, Rostock and Gambro Renal Products, Denver, Colorado. Grifols Inc. Los Angeles supplied the albumin solution

[y] One author affiliation: Clinical Research, Fresenius Medical Care, Bad Homburg, Germany and Conduct of the study was supported by Fresenius Medical Care

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[ad] One author affiliation is Vital Therapies, San Diego, CA, USA and study is listed as a publication on Vital Therapies Inc. website

[ae] The study was financed by Vital Therapies, Inc., San Diego, CA

48, 59, 60]. We present characteristics of included trials in Table 1.

Risk of bias assessment

Of the 25 studies, 21 were published as full articles and 4 as abstracts. We did not consider lack of blinding of participants as high risk of bias since it is impossible to ensure blinding and the outcomes were objective; therefore, less likely to be affected by lack of blinding [61]. Fourteen studies were adjudicated as overall low risk of bias [36, 37, 39, 44, 46, 49–52, 54, 55, 57, 58, 60], 10 were adjudicated as overall unclear risk of bias [40–43, 45, 47, 48, 53, 56, 59] and 1 adjudicated as overall high risk of bias [38]. We present the details of risk of bias assessment in ESM Fig. S2 and Table 4.

Assessment of quality of the evidence

We present the details of our assessment of the certainty of evidence for each outcome according to the GRADE approach in Table 2.

Main outcomes

Mortality

Twenty-four RCTs enrolling 1778 patients reported on mortality [36–60]. The use of ECLS probably reduces mortality (RR 0.84; 95% CI 0.74, 0.96, $P=0.01$, I^2=33%, moderate certainty) (Fig. 1). Publication bias was not detected by visually inspecting funnel plot and by Egger's test ($P=0.417$) (ESM Fig. S3).

Bridging to liver transplant

The data reported in individual trials were either incomplete or not reported; therefore, we were not able to perform a meta-analysis for this outcome.

Hepatic encephalopathy

Twelve RCTs enrolling 417 patients reported on HE [36, 38, 42–46, 48, 49, 53, 58, 59]. The use of ECLS may improve HE compared to usual care (RR 0.71; 95% CI 0.60, 0.84, $P<0.0001$, I^2 0%, low certainty) (Fig. 2). We downgraded the certainty evidence by one point as publication bias was suspected by visually inspecting funnel plot and by Egger's test ($P=0.041$) (ESM Fig. S4).

Adverse events

Nine RCTs enrolling 748 patients reported on hypotension [39, 42–44, 46, 49, 51, 55, 60]. The effect of ECLS on the risk of hypotension was uncertain [RR 1.46; 95% CI (0.98, 2.2), $P=0.07$, $I^2=15\%$, low certainty]. Eleven RCTs enrolling 1031 patients reported on bleeding, with little to no difference between the two groups (RR 1.21; 95% CI 0.88, 1.66, $P=0.25$, $I^2=31\%$, moderate certainty) [36, 42–44, 46, 48–50, 55, 57, 60]. Five RCTs enrolling 564 patients reported on thrombocytopenia [39, 44, 51, 57, 60]; the use of ECLS was associated with increased risk of thrombocytopenia (RR 1.62; 95% CI 1.0, 2.64, $P=0.05$, $I^2=62\%$, very low certainty). Only one RCT with 16 patients reported on line infections (RR 1.92; 95% CI 0.11, 33.44, $P=0.65$, low certainty) [46] (Fig. 3). None of the included trials reported on citrate toxicity.

Subgroup analyses

We conducted four subgroup analyses, the first was by type of liver failure (ALF versus ACLF). Thirteen RCTs enrolled 738 patients with ALF (RR 0.90; 95% CI 0.75, 1.08, $P=0.27$, $I^2=25\%$) [37–39, 41–43, 45, 48, 52, 53, 56, 57, 59] and 13 RCTs enrolled 1040 patients with ACLF (RR 0.78; 95% CI 0.66, 0.93, $P=0.006$, $I^2=30\%$) [36, 40,

Table 2 GRADE evidence profile

Certainty assessment							No. of patients		Effect		Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECLS	Control	Relative (95% CI)	Absolute (95% CI)	
Mortality											
24	Randomised trials	Not serious[a]	Not serious	Not serious	Serious[b]	None	337/901 (37.4%)	403/877 (46.0%)	RR 0.84 (0.74–0.96)	74 fewer per 1000 (from 119 fewer to 18 fewer)	⨁⨁⨁◯ MODERATE
Hepatic encephalopathy											
12	Randomised trials	Not serious[a]	Not serious	Not serious	Serious[c]	Publication bias strongly suspected	70/213 (32.9%)	116/204 (56.9%)	RR 0.71 (0.60–0.84)	165 fewer per 1000 (from 227 fewer to 91 fewer)	⨁⨁◯◯ LOW
Hypotension											
9	Randomised trials	Not serious[a]	Not serious	Serious[d]	Serious[e]	None	72/365 (19.7%)	50/383 (13.1%)	RR 1.46 (0.98–2.20)	60 more per 1000 (from 3 fewer to 157 more)	⨁⨁◯◯ LOW
Bleeding											
11	Randomised trials	Not serious[a]	Not serious	Not serious	Serious[f]	None	120/507 (23.7%)	99/524 (18.9%)	RR 1.21 (0.88–1.66)	40 more per 1000 (from 23 fewer to 125 more)	⨁⨁⨁◯ MODERATE
Thrombocytopenia											
5	Randomised trials	Not serious[a]	Serious[g]	Serious[d]	Serious[h]	None	107/284 (37.7%)	68/280 (24.3%)	RR 1.62 (1.00–2.64)	151 more per 1000 (from 0 fewer to 398 more)	⨁◯◯◯ VERY LOW
Line infection											
1	Randomised trials	Not serious[a]	Not serious	Not serious	Very serious[i]	None	2/12 (16.7%)	0/4 (0.0%)	RR 1.92 (0.11–33.44)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW

CI confidence interval, *RR* risk ratio

[a] We did not downgrade for unblinding of intervention as it is not possible. However, the outcomes are objective

[b] We downgraded for imprecision by one point as Trial Sequential Analysis (TSA) estimates yielded difference point estimate and a wider confidence interval; (RR 0.84, 95% CI 0.72–0.97) and 95.4% of required information size (RIS) achieved

[c] We downgraded for imprecision by 1 point as TSA estimates yielded difference point estimate and a wider confidence interval; 0.68 (95% CI 0.44, 1.05) and only 39% of RIS achieved

[d] Hypotension in itself is a surrogate outcome

[e] We downgraded by one point for imprecision as confidence interval includes significant benefit and harm (0.98, 2.2)

[f] We downgraded by one point for imprecision as confidence interval includes significant benefit and harm (0.88, 1.66)

[g] Significant heterogeneity detected ($I^2 = 62\%$)

[h] We downgraded by one point for imprecision as confidence interval includes significant benefit and harm (0.7, 1.09)

[i] We downgraded by two points for imprecision. Confidence interval included significant benefit and harm and very wide CI

44–47, 49, 50, 54, 55, 58–60]. Although the estimates for ALF subgroup were imprecise, the interaction test did not suggest a subgroup difference ($P = 0.28$) for mortality (ESM Fig. S5). The second analysis was by type of ECLS (artificial versus bio-artificial liver support). Nineteen trials (1308 patients) (1308 patients) [36–38, 41, 42, 44–46, 48–50, 52–59] and five trials (470 patients) [39, 40, 43, 47, 60] used artificial and bio-artificial liver support systems, respectively. We did not find a subgroup difference for mortality ($P = 0.55$) (ESM Fig. S6). The third subgroup analysis was by risk of bias (low versus unclear and high). Eleven trials (1096 patients) were at low risk of bias [36, 37, 39, 44, 46, 49, 54, 55, 57, 58, 60] and 13 trials (682 patients) were at unclear risk of bias [38, 40–43, 45, 47, 48, 50, 52, 53, 56, 59]. The risk of bias did not significantly influence risk of death ($P = 0.80$) (ESM Fig. S7). The

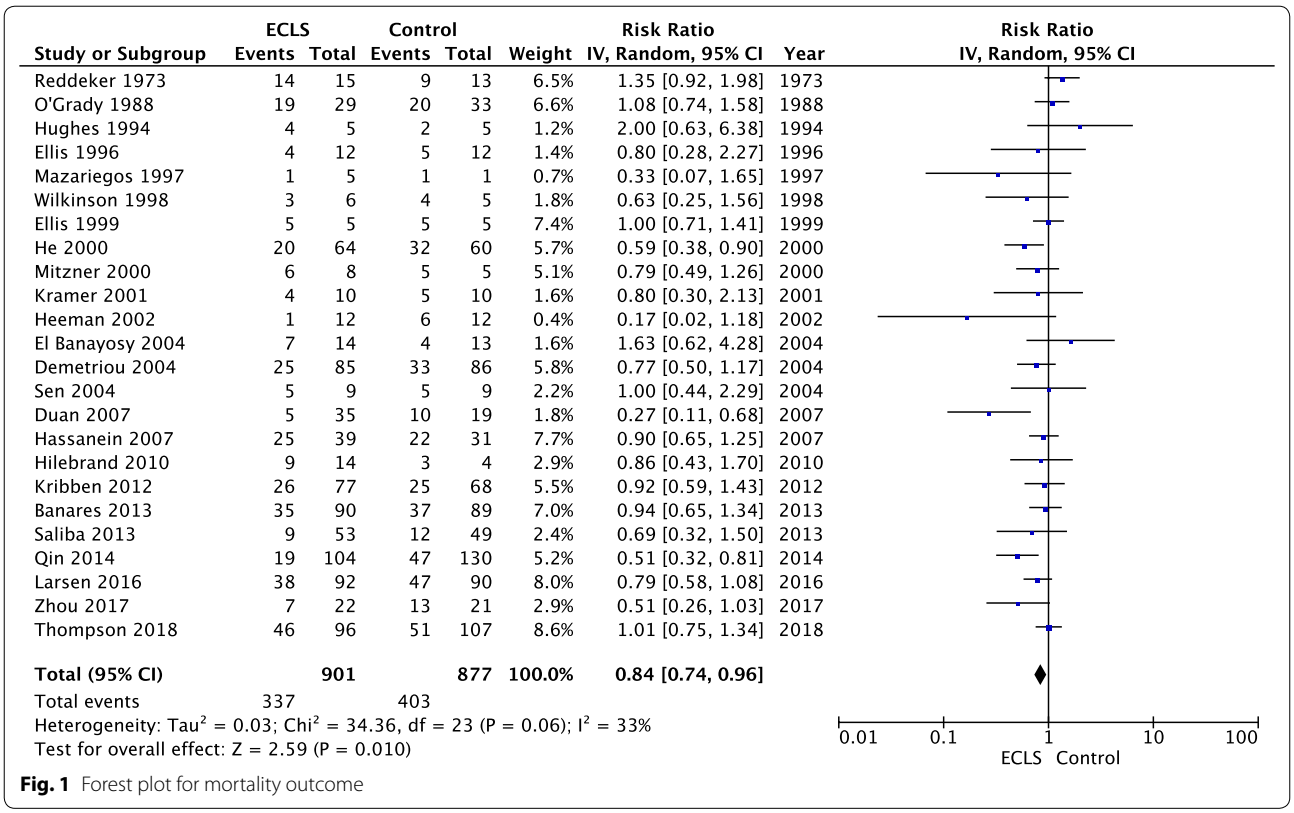

Fig. 1 Forest plot for mortality outcome

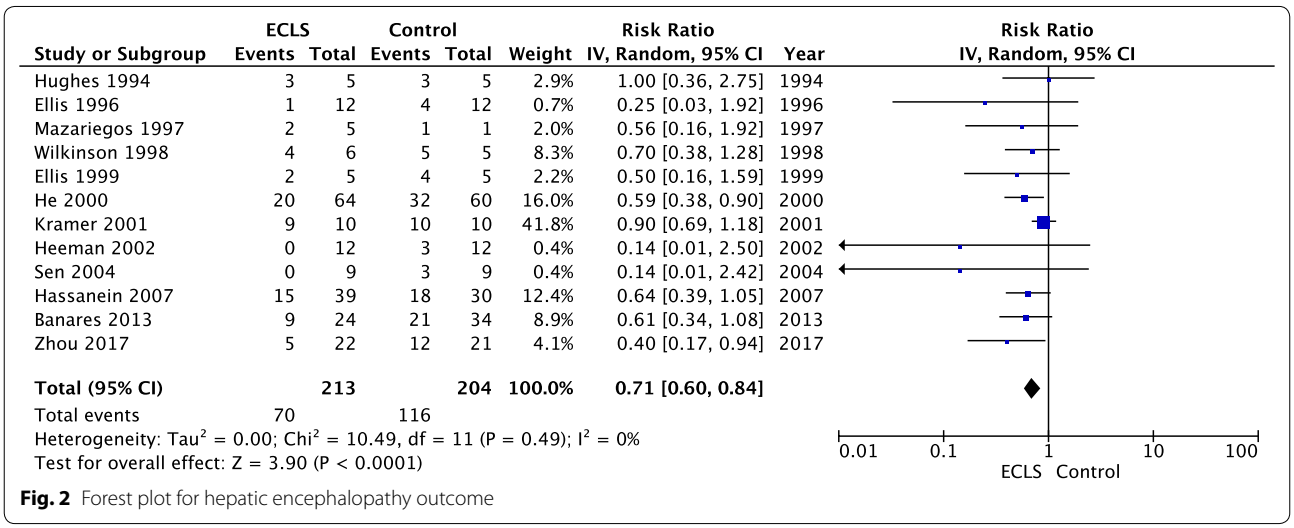

Fig. 2 Forest plot for hepatic encephalopathy outcome

fourth subgroup analysis was by funding source (industry versus academic), this analysis was decided post hoc. Nine trials (692 patients) [39, 40, 42, 44, 47, 48, 50, 59, 60] were industry funded, and 15 trials (1086 patients) [36–38, 41, 43, 45, 46, 49, 52–58] were funded by academic sources. We observed no significant subgroup differences (ESM Fig. S8). We present all subgroup analyses in the supplement.

Sensitivity analysis

A sensitivity analysis excluding four studies published in abstract form [40, 41, 47, 53] yielded similar results as the primary analyses for mortality [RR 0.87; 95% CI (0.75, 1.00), $P=0.05$, $I^2=37\%$, moderate certainty] (ESM Fig. S9), and HE (RR 0.70; 95% CI 0.58, 0.84, $P=0.0006$, $I^2=0\%$, low certainty) outcomes (ESM Fig. S10). We performed a post hoc sensitivity excluding the study by

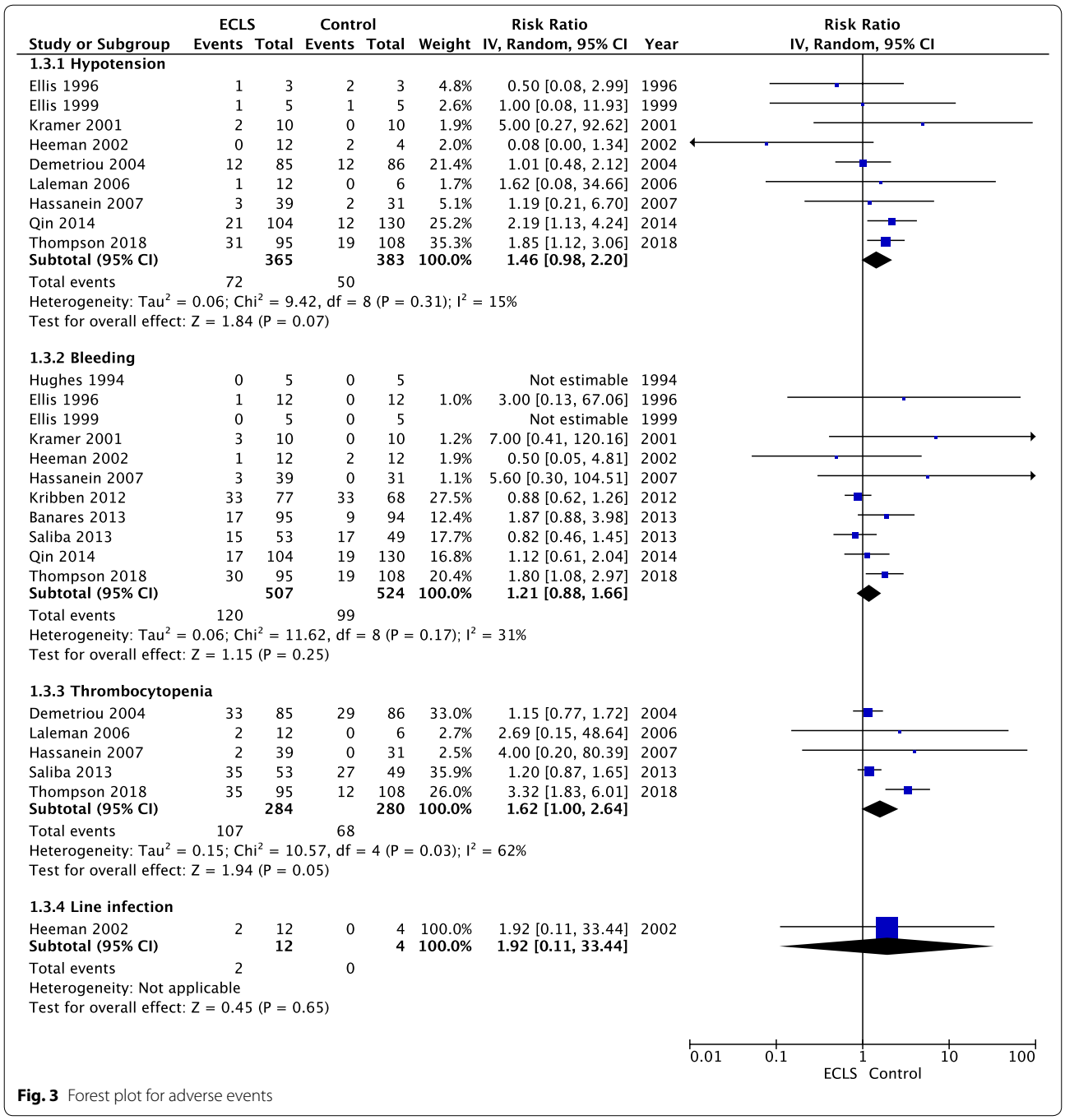

Fig. 3 Forest plot for adverse events

Zhou et al. as the control group composed of patients who declined consent to any of the two intervention arms (plasma exchange versus plasma exchange with albumin dialysis) [38]. The results remained similar to primary analyses for both mortality and hepatic encephalopathy (ESM Figs. S11, S12).

Trial sequential analysis

For mortality outcome; post hoc TSA concurs with the conventional analysis and provides a reliable estimate that the use of ECLS is associated with a reduced mortality risk compared to control (TSA-adjusted RR 0.84, 95% CI 0.73, 0.97), and that the RIS has been achieved

(ESM Fig S13). Whereas, for HE outcome, post hoc TSA showed that the cumulative Z score crossed the adjusted boundaries for benefit ($Z > 1.96$), the RIS has not been reached (39%), indicating inconclusive benefit for ECLS in the reduction of HE using (TSA-adjusted RR 0.71 95% CI 0.57, 0.89) (ESM Fig. S14). Power of 80% and RRR of 20% were used for TSA.

Discussion

This systematic review and meta-analysis of 25 RCTs provides moderate certainty evidence on reduction of mortality with ECLS. In ALF and ACLF patients, ECLS may reduce mortality by 16%, which translates into 74 fewer deaths per 1000 patients, and an NNT of 22 and 16 in ALF and ACLF population, respectively. The effect on mortality was more prominent with artificial devices than with bio-artificial devices, and in ACLF than in ALF population. In addition, our results show that ECLS may reduce HE in patients with liver failure.

Although we included all types of liver failure in this review, there are differences in pathophysiology, causes, and prognosis within this population. Unlike ACLF patients, ALF patients have no pre-existing liver disease [21, 28]. Most common causes of ALF include acetaminophen toxicity (46.3%), indeterminate (12.2%) and other drugs (10.8%) in a recent report from the United States [28], compared to bacterial infection (39.1%) and alcohol (22.9%) among 417 cases of ACLF in Europe [21]. In addition, liver transplantation might not be an option for many patients with ACLF due to advanced age, active alcohol intake, other comorbidities and associated organ failure [21]. ALF patients are more likely to get liver transplants sooner than ACLF patients [57, 62]. Furthermore, ACLF patients had higher overall mortality than ALF patients (260 versus 188 per 100 waitlist-years) [62]. This could explain the larger mortality reduction in ACLF population, as they have a higher baseline risk of death, less likely to receive definitive therapy with liver transplant and a smaller chance of spontaneous resolution (15–50%) [21].

The use of ECLS devices appeared to be safe, we did not observe a significant increase in the risk of adverse events. However, thrombocytopenia was more common with ECLS, but the certainty of data was very low. Finally, no studies reported on citrate toxicity.

Although there are several published meta-analyses on this topic, we included more trials (25 total, 24 for mortality) than any previous meta-analyses [3–11, 63] (ranging between 4 and 19), which improved the precision of our findings.

Our findings have important limitations. The duration of follow-up for mortality outcome varied between studies (Table 1), although the statistical heterogeneity was below our pre-specified threshold, it is a potential source of clinical heterogeneity. The results of post hoc TSA (power 80% and RRR 20%) revealed potential imprecision with wider adjusted 95% CI for HE outcome as the RIS has not been achieved. In addition, several studies were industry funded, raising concerns about potential bias. Although our post hoc subgroup analysis did not support this possibility, subgroup analyses are often underpowered. Reporting of some outcomes such as liver transplant was not clear. It was not possible to determine the number of patients listed for liver transplant in each of studies. In addition, the population was heterogeneous with different causes of liver failure, and individual patient data were not available for various subgroups. Further studies are needed to identify which subgroups would benefit the most from ECLS. Lastly, ECLS devices are expensive and are not available at most centers, given the additional direct costs of the intervention, policymakers need to better understand the cost-effectiveness of ECLS in liver failure before making it available for routine use in practice. Hessel et al. studied the cost-effectiveness in a cohort of 149 patients with ACLF, of which 67 (44.9%) were treated with MARS and found that the incremental cost per life year gained was 30% less for MARS [64]. However, data on cost-effectiveness of other modalities are lacking.

Conclusions

Our meta-analysis shows that ECLS may reduce death and improve HE in patients with liver failure. Before ECLS can be routinely used in practice, future RCTs are needed to determine the magnitude of effect, the most effective modality, and the subgroup that would benefit the most from ECLS.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05783-y) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
All authors reported no conflicts of interest.

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