SYSTEMATIC REVIEW

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Artificial Liver Support Systems in Acute Liver Failure and Acute-on-Chronic Liver Failure: Systematic Review and Meta-Analysis

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OBJECTIVES: To systematically review the safety and efficacy of nonbiological (NBAL) or biological artificial liver support systems (BAL) and whole-organ extracorporeal liver perfusion (W-ECLP) systems, in adults with acute liver failure (ALF) and acute-on-chronic liver failure (ACLF).

DATA SOURCES: Eligible NBAL/BAL studies from PubMed/Embase searches were randomized controlled trials (RCTs) in adult patients with ALF/ACLF, greater than or equal to ten patients per group, reporting outcomes related to survival, adverse events, transplantation rate, and hepatic encephalopathy, and published in English from January 2000 to July 2023. Separately, we searched for studies evaluating W-ECLP in adult patients with ALF or ACLF published between January1990 and July 2023.

STUDY SELECTION AND DATA EXTRACTION: Two researchers independently screened citations for eligibility and, of eligible studies, retrieved data related to study characteristics, patients and interventions, outcomes definition, and intervention effects. The Cochrane Risk of Bias 2 tool and Joanna Briggs Institute checklists were used to assess individual study risk of bias. Meta-analysis of mortality at 28–30 days post-support system initiation and frequency of at least one serious adverse event (SAE) generated pooled risk ratios (RRs), based on random (mortality) or fixed (SAE) effects models.

DATA SYNTHESIS: Of 17 trials evaluating NBAL/BAL systems, 11 reported 28–30 days mortality and five reported frequency of at least one SAE. Overall, NBAL/BAL was not statistically associated with mortality at 28–30 days (RR, 0.85; 95% CI, 0.67–1.07; $p = 0.169$) or frequency of at least one SAE (RR, 1.15; 95% CI, 0.99–1.33; $p = 0.059$), compared with standard medical treatment. Subgroup results on ALF patients suggest possible benefit for mortality (RR, 0.67; 95% CI, 0.44–1.03; $p = 0.069$). From six reports of W-ECLP (12 patients), more than half (58%) of severe patients were bridged to transplantation and survived without transmission of porcine retroviruses.

CONCLUSIONS: Despite no significant pooled effects of NBAL/BAL devices, the available evidence calls for further research and development of extracorporeal liver support systems, with larger RCTs and optimization of patient selection, perfusion durability, and treatment protocols.

KEYWORDS: acute liver failure; acute-on-chronic liver failure; extracorporeal liver perfusion; extracorporeal liver support; systematic literature review

Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) are challenging conditions with considerable risk of complication and death and are among the most frequent reasons for admission to intensive care (1–4). The release of toxins and overproduction of cytokines due to liver necrosis may result in severe systemic inflammation and subsequent multiple organ failure (2, 5). For severe cases with poor prognosis, transplantation

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KEY POINTS

Question: What is the safety and efficacy of nonbiological (NBAL) or biological artificial liver support systems (BAL) and whole-organ extracorporeal liver perfusion (W-ECLP) systems, in adults with acute liver failure (ALF) and acute-on-chronic liver failure?

Findings: We found no statistically significant pooled effect of NBAL/BAL on mortality at 28–30 days or frequency of at least one serious adverse event; ALF results suggest mortality reduction. More than half of severe ALF patients receiving W-ECLP were bridged to transplantation and survived.

Meaning: Further research should consider interspecies liver physiology and the supporting cells' role and be conducted on an optimized population with adequate and monitored perfusion protocols.

remains the most effective treatment but organ availability is a major limitation (6).

Extracorporeal liver support systems may provide patient support until an organ becomes available or facilitate regeneration with recovery without the need for transplantation. The systems evaluated in several studies including randomized controlled trials (RCTs) are nonbiological artificial liver support systems (NBAL) relying on membranes, adsorbents (e.g., albumin), and other materials to clear blood toxins, and biological artificial liver support systems (BAL), which are ex vivo liver perfusion devices incorporating hepatocytes, combining detoxification with synthetic and biochemical production (7–9). Whole-organ extracorporeal liver perfusion (W-ECLP), that is, using human or animal livers ex vivo to help bridge patients to transplantation, has been evaluated since 1990 (10). Research interest in xenoperfusion has been recently reinvigorated, alongside xenotransplantation, following the advent of gene editing and co-stimulation blockade mechanisms. Hence, it is appropriate to review the clinical trials of prior systems, to learn lessons that might inform future research in this new era (10).

To our knowledge, there is no comprehensive review of the entire spectrum of liver support systems–NBAL, BAL, and W-ECLP (7, 11–14). This systematic review aims to explore the safety and efficacy of artificial liver support systems in adults with ALF or ACLF and to summarize the current developmental landscape of porcine and human W-ECLP in these conditions.

METHODS

This systematic review with meta-analysis (PROSPERO: CRD42023451795) followed the Meta-analysis Of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the Cochrane Handbook recommendations (15–17). No institutional review board/ethics approval was required.

Eligibility Criteria

Two separate search strategies were defined. NBAL/BAL eligible studies were English-language RCTs evaluating NBAL or BAL devices in adult patients with ALF or ACLF, with greater than or equal to ten patients per group (to avoid overestimation of treatment effects [18, 19]), reporting outcomes related to survival, adverse events, transplantation rate, or changes in hepatic encephalopathy, and published between January 1, 2000, and July 31, 2023 (**Table S1**, http://links.lww.com/CCX/B446). Given the lack of RCTs and paucity of data related to W-ECLP systems, the second search considered all studies irrespective of design, evaluating W-ECLP in adult patients with ALF or ACLF, reporting survival or other clinical outcomes, published in English between January 1990 and July 2023. For both searches, reports limited to liver failure due to primary nonfunction after liver transplantation, or those evaluating isolated hepatocyte or stem cell transplantation, were excluded.

Search Strategy and Data Extraction

Searches were conducted in PubMed/MEDLINE and Embase databases using predefined terms (Table S1, http://links.lww.com/CCX/B446). Two researchers (M.F., W.H.T.) independently screened titles/abstracts and then the full text of retrieved records, and the reference lists of eligible records and recent reviews. Data—related to characteristics of studies, patients and interventions, definition of outcomes, and reported intervention effects (details in **Supplemental Material**, http://links.lww.com/CCX/B446)—were retrieved from eligible studies into a predefined Excel (Microsoft, Redmond, Washington) file and cross-checked independently by two reviewers; discrepancies were adjudicated.

Qualitative Synthesis and Outcomes of Interest

All eligible records were included in the qualitative synthesis of NBAL/BAL and W-ECLP systems. All outcomes related to survival and transplantation and safety were summarized in tables. Following assessment of the NBAL/BAL studies' characteristics, the most frequently reported outcomes were cumulative mortality 28–30 days post-support system initiation and the frequency of at least one serious adverse event (SAE) during the study period, which were deemed feasible for meta-analysis. For studies reporting survival based on Kaplan-Meier curves, probabilities were assumed to be approximately equal to the respective proportion at 28–30 days.

Risk of Bias Assessment

Two reviewers (M.F., W.H.T.) independently assessed the risk of bias in individual trials using the Cochrane risk-of-bias tool for randomized trials (RoB2) (20). For each outcome, trials were classified to be at "Low risk," "Some concerns," or "High" risk of bias, based on the assessment of the five RoB2 domains through which bias might occur.

Even though the eligible W-ECLP literature consisted of case reports/series, with outcomes too heterogeneous for meta-analysis, the risk of bias was assessed using the Joanna Briggs Institute checklists (21).

Meta-analysis

Meta-analyses were conducted using Comprehensive Meta-Analysis, Version 4 (Biostat, Englewood, NJ). As the selected outcomes are dichotomous, pooled risk ratios (RRs) and corresponding 95% CI were reported, based on fixed- or random-effects (DerSimonian and Laird [22]) models, according to the between-study effects variability. The inverse variance method was used to estimate study weights in both fixed- and random-effects approaches (22). Publication bias was investigated through visual inspection of funnel plots and Egger's regression (23). Analyses planned a priori were performed to further explore results, including a sensitivity analysis excluding studies published before 2010, and subgroup analyses stratified by device category (BAL vs. NBAL), type of liver failure (for both outcomes), and by timepoint of assessment (i.e., 5–10 vs. 90–91 d) for the SAE outcome. All p values were based on two-sided tests, and a significance level of 0.05 was assumed.

RESULTS

Characteristics of RCTs Evaluating NBAL or BAL

After excluding noneligible studies (**Figs. S1** and **S2**, http://links.lww.com/CCX/B446), we identified 17 individual NBAL/BAL studies (**Tables S2** and **S3**, http://links.lww.com/CCX/B446). Twelve studies evaluated NBAL or BAL in a total of 1399 patients with ACLF (24–35), and five RCTs evaluated NBAL or BAL in 522 patients with ALF (36–40). In the ACLF population, the evaluated systems were the Molecular Adsorbent Recirculating System (MARS) alone or with plasma exchange (PE), PE alone, DIALIVE (https://aliver.info/project/dialive-concept/), Biologic-DT (Hemocleanse, Lafayette, IN), and Prometheus (Fresenius Medical Care, Bad Homburg, Germany), and the BAL system extracorporeal cellular therapy - ELAD (Vital Therapies, London, United Kingdom). In the ALF population, the systems evaluated were MARS, PE, and HepatAssist (Circe Biomedical, Lexington, MA). Almost all studies compared NBAL/BAL against standard medical therapy (SMT), except for Huang et al (29), which evaluated the efficacy of combining PE to MARS vs. MARS in patients with ACLF.

The number of sessions and duration of the intervention varied. The mean number of MARS sessions ranged from 3 to 7, and cumulative support duration from 16 hours up to 60 hours. HepatAssist was used, on average, in three sessions (6 hr per session) (36), while ELAD was used during one single session of which Duan et al (26) reported a mean duration of 68 hours.

The number of patients by treatment group ranged from 10 to 140. Age, sex, or liver etiology did not differ between groups, except in one study where MARS patients were statistically younger (49 vs. 56 yr in the SMT group) (27).

Survival and Transplantation Outcomes Following NBAL or BAL

A total of 11 studies (two ALF, nine ACLF) investigating the effects of NBAL/BAL devices vs. SMT reported mortality or survival estimates at 28–30 days (**Table 1**). Statistically significant reductions of mortality at 28–30 days were reported with MARS (8.3% vs. 50% in

TABLE 1.

All-Cause Mortality/Overall Survival Outcomes Reported in Nonbiological/Biological Artificial Liver Support Systems Trials

Author (Publication Year)	Intervention | Comparator	*n*[a]	Outcome	Assessment Timepoint	% With Event[b]	*p*[c]
Acute-on-chronic liver failure population–biological artificial liver support systems						
Teperman (33) (2012)	ELAD | SMT	25 | 28	Survival proportion	Day 30	52.0% | 67.9%	NS
				Day 90	44.0% | 42.9%	NR
Duan et al (26) (2018)	ELAD | SMT	32 | 17	Mortality proportion	Day 28	12.5% | 17.6%	NR
				Day 84	28.1% | 23.5%	NR
Thompson et al (34) (2018)	ELAD | SMT	96 | 107	Survival proportion	Day 28	76.0% | 80.4%	NR
				Day 91	59.4% | 61.7%	NR
Acute-on-chronic liver failure population–nonbiological artificial liver support systems						
Kramer et al (30) (2001)	Biologic-DT | SMT	10 | 10	Mortality proportion	Day 30	60.0% | 60.0%	1.0
Heemann et al (28) (2002)	MARS | SMT	12 | 12	Mortality probability	Day 30	8.3% | 50.0%	< 0.05
				Day 180	50.0% | 66.7%	0.069
Hassanein et al (27) (2007)	MARS | SMT	39 | 31	Mortality proportion	Day 5	13.0% | 16.0%	NR
				Day 10	23.1% | 22.6%	NS
				Day 30	51.5% | 48.3%	NR
				Day 180	64% | 71%	NS
Yu et al (35) (2008)	PE | SMT	140 | 140	Mortality proportion	Day 90	67.1% | 91.4%	NR
Huang et al (29) (2012)	PE + MARS | MARS	60 | 60	Mortality proportion	Day 30	10.0% | 11.7%	0.769
Kribben et al (31) (2012)	Prometheus | SMT	77 | 68	Survival probability	Day 28	66.0% | 63.0%	0.70
				Day 90	47.0% | 38.0%	0.35
Qin et al (32) (2014)	PE | SMT	104 | 130	Survival probability	Day 30	81.7% | 63.8%	NR
				Day 90	59.6% | 46.9%	0.016
				5 yr	43.3% | 30.8%	0.013
Agarwal et al (24) (2023)	DIALIVE | SMT	17 | 15	Mortality proportion	Day 28	23.5% | 20.0%	NR
				Day 90	29.4% | 26.7%	NR
Acute liver failure population–biological artificial liver support systems						
Demetriou et al (36) (2004)	HepatAssist | SMT	73 |74	Survival proportion	Day 30	72.6% | 59.5%	0.117

(*Continued*)

TABLE 1. (*Continued*)
All-Cause Mortality/Overall Survival Outcomes Reported in Nonbiological/Biological Artificial Liver Support Systems Trials

Author (Publication Year)	Intervention | Comparator	*n*[a]	Outcome	Assessment Timepoint	% With Event[b]	*p*[c]
Acute liver failure population–nonbiological artificial liver support systems						
El Banayosy et al (37) (2004)	MARS | SMT	14 | 13	Survival proportion	End of study	50.0% | 30.8%	NS
Saliba et al (40) (2013)	MARS | SMT	53 | 49	Survival probability	Day 30	90.6% | 85.7%	NR
				12-mo	83.0% | 75.5%	0.35

ELAD = extracorporeal cellular therapy, MARS = Molecular Adsorbent Recirculating System, NR = not reported, NS = nonsignificant, PE = plasma exchange, SMT = standard medical therapy.
[a]Values refer to the number of participants.
[b]Values refer to the percentage of patients with the event in the intervention group and the comparator group.
[c]*p* values as reported by the trials' authors.

SMT group; $p < 0.05$) (28) and after adjusting for confounding variables, for example, transplantation, with HepatAssist (RR = 0.56; $p = 0.048$) (36). In addition, Qin et al (32) described significant differences between PE and SMT survival probability at day 90 ($p = 0.016$).

Among the four studies reporting transplant-free survival at 84–90 days, statistically significant differences were observed with ELAD in patients with ACLF (26), and PE in patients with ALF (**Table S4**, http://links.lww.com/CCX/B446) (38). Maiwall et al (39) also reported favorable results with PE in the ALF population at 28–30 days.

Of 11 studies reporting mortality at 28–30 days, seven were classified with low risk of bias and four with some concerns of bias (**Fig. S3**, http://links.lww.com/CCX/B446). Significant heterogeneity across studies was not observed (Q-test $p = 0.178$, $I^2 = 28\%$); based on the observed heterogeneity and between-study variance ($\tau^2 = 0.041$), the pooled RR estimate was calculated using the DerSimonian-Laird random-effects model. The visual inspection of the funnel plot (Fig. S3, http://links.lww.com/CCX/B446) and Egger's regression did not suggest publication bias ($p = 0.774$).

We found no statistically significant effect on mortality at 28–30 days with the use of NBAL/BAL compared with SMT (RR, 0.85; 95% CI, 0.67–1.07; $p = 0.169$; 95% prediction interval, 0.50–1.44; **Fig. 1**). Similar results were found when considering only studies published after 2010 (RR, 0.89; 95% CI, 0.64–1.25; $p = 0.512$).

In the subgroup of patients with ALF, the pooled RR of NBAL/BAL was 0.67 (95% CI, 0.44–1.03; $p = 0.069$) and, in patients with ACLF, we found an RR = 0.90 (95% CI, 0.68–1.19; $p = 0.448$). The subgroup analysis by type of system returned no statistically significant effects with BAL (RR, 0.99; 95% CI, 0.66–1.50; $p = 0.971$) or NBAL (RR, 0.77; 95% CI, 0.58–1.03; $p = 0.076$), compared with SMT.

Safety Outcomes Following NBAL or BAL

Safety outcomes were commonly reported as the frequency of at least one SAE/treatment-emergent SAE or at least one AE/treatment-emergent AE (**Table S5**, http://links.lww.com/CCX/B446). At 5–10 days, the proportion of patients with at least one SAE ranged from 25.9% in the SMT group of the study by Hassanein et al (27) to 64.7% in the DIALIVE group from the study by Agarwal et al (24). At 90–91 days, the proportions of at least one

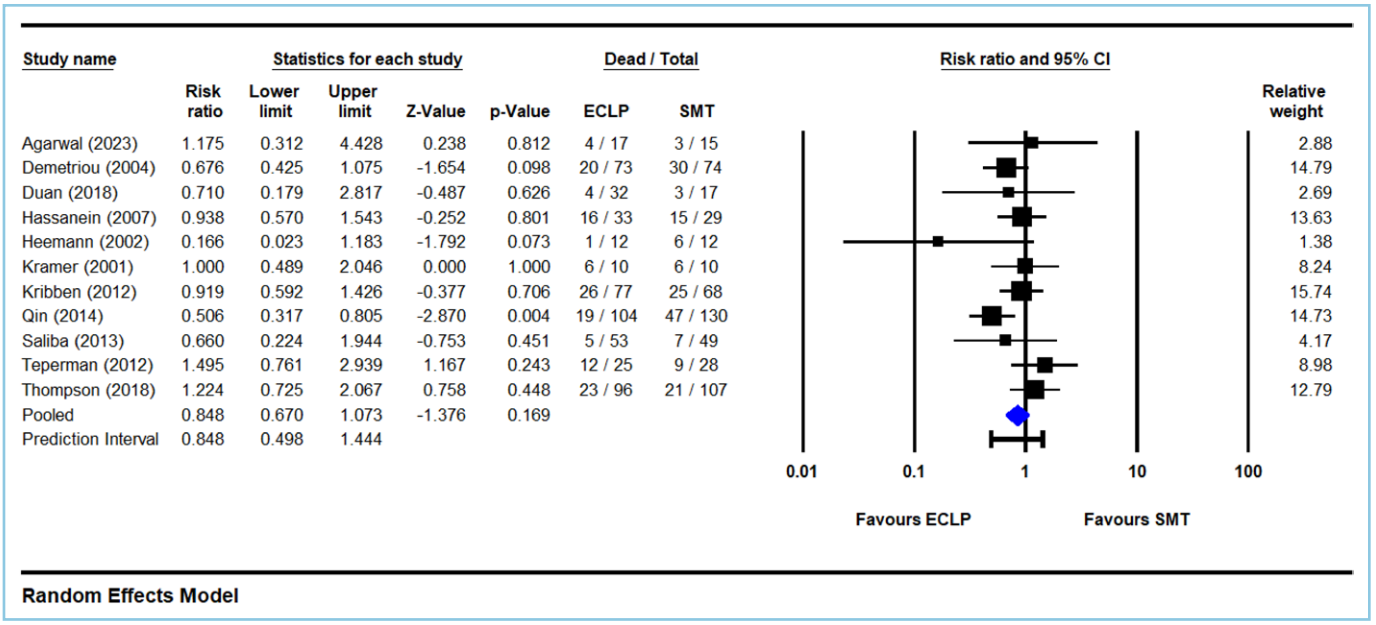

Figure 1. *Forest plot*—mortality at 28–30 d. ECLP = extracorporeal liver perfusion, SMT = standard medical therapy.

SAE ranged from 53.1% in the SMT group of the study by Teperman (33) to 76.8% in the ELAD group of the study by Thompson et al (34).

Studies also reported the most frequent AEs/SAEs or selected AEs of interest, although with some heterogeneity in definitions. Across studies, the most reported events were bleeding, bacterial infection, hypotension, and thrombocytopenia. No statistically significant differences were reported between interventional and SMT groups, except in the study by Thompson et al (34), with the ELAD group showing statistically significantly higher proportions of the AEs anemia (44% vs. 16%; $p < 0.05$), thrombocytopenia (35% vs. 11%; $p < 0.05$), coagulopathy (31% vs. 12%; $p < 0.05$), and hypotension (31% vs. 17%; $p < 0.05$), and in the study by Qin et al (32), which reported more AEs of skin rash (29.6% vs. 6.9%; $p < 0.01$) and hypotension (20.2% vs. 9.2%; $p = 0.02$) among patients receiving PE support. In addition, Heemann et al (28) observed a lower proportion of cases with worsening renal function among patients receiving MARS (8.3% vs. 58.3% in the SMT group; $p < 0.05$).

A total of five studies reported the proportion of patients experiencing at least one SAE, classified with some concerns on the risk of bias (Fig. S2, http://links.lww.com/CCX/B446). Due to the low level of heterogeneity (Q-test $p = 0.587$; $I^2 = 0.00\%$), and the between-study variance (τ) being approximately equal to 0, a fixed-effects model was used. The funnel plot and Egger's regression did not suggest publication bias ($p = 0.310$; and **Fig. S4**, http://links.lww.com/CCX/B446).

Compared with SMT, NBAL/BAL systems showed no statistically significant effect on frequency of at least one SAE (RR, 1.15; 95% CI, 0.99–1.33; $p = 0.059$; **Fig. 2**). When considering only the studies published after 2010, the pooled RR was 1.12 (95% CI, 0.97–1.30; $p = 0.137$).

No statistically significant effect was observed in the subgroup of BAL (RR, 1.11; 95% CI, 0.99–1.30; $p = 0.171$) nor NBAL devices (RR, 1.51; 95% CI, 0.94–2.45; $p = 0.092$). In addition, no statistically significant effect was observed in the subgroup of studies reporting frequency of at least one SAE at days 5–10 (RR, 1.41; 95% CI, 0.95–2.10; $p = 0.091$) nor at days 90–91 (RR, 1.12; 95% CI, 0.95–1.30; $p = 0.172$).

Qualitative Synthesis of Studies Evaluating W-ECLP

Regarding the W-ECLP search, 119 records were screened and seven reports of six studies were included (**Fig. S5**, http://links.lww.com/CCX/B446). These single-center studies (24, 41–45) described the use of W-ECLP in 12 eligible adult patients with ALF ($n = 11$) or ACLF (**Table S6**, http://links.lww.com/CCX/B446). The most frequent W-ECLP origin was porcine ($n = 10$), and sessions took between 0.5 and 39 hours (median = 15 hr). The risk of bias was classified as minor and all studies were considered for qualitative synthesis (**Table S7**, http://links.lww.com/CCX/B446).

Seven patients (58.3%) survived, all receiving transplantation. Two patients had support withdrawn after

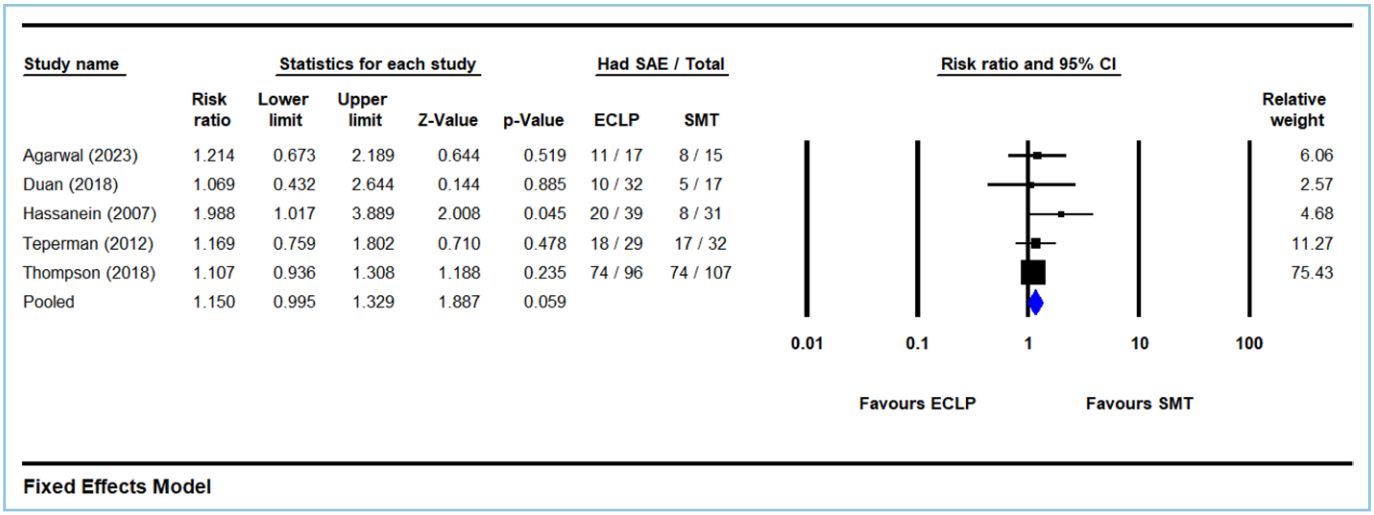

Figure 2. *Forest plot*—at least one serious adverse event (SAE). ECLP = extracorporeal liver perfusion, SMT = standard medical therapy.

contraindication for transplantation was observed. Among patients who died before or during transplantation (n = 3), one developed sepsis, another presented increased intracranial pressure despite the perfusion, and a third had brainstem herniation during transplantation due to excessive correction of hyponatremia. This last case had no information about encephalopathy severity while the other two deaths reported grade V encephalopathy at W-ECLP initiation.

Among survivors, clinical biomarkers (e.g., total bilirubin and ammonia) showed improved results after perfusion. Horslen et al (42) reported no relevant differences in these biomarkers between W-ECLP of human or porcine origin. Examination of pig livers showed minimal lymphocytic infiltrates (41–44) with hepatocyte necrosis reported in two studies (42, 44, 46), but deemed minor or absent in the other two cases (41, 43). Mild deposition of immunoglobulin M (IgM), immunoglobulin G (IgG), and/or complement in W-ECLP pig livers was reported in four out of five studies with immunological assessment (42–44, 46). One study analyzed the peripheral mononuclear cells of two patients who underwent successful W-ECLP with transgenic pig livers and did not identify porcine endogenous retrovirus DNA sequences (46).

DISCUSSION

In our systematic review of the safety and efficacy of artificial liver support systems, we have not found statistically significant pooled effects of NBAL/BAL devices compared with SMT. Still, the potential benefit in the ALF population (i.e., reduction of 33% on 28–30 d mortality; p = 0.069) demands a better understanding of these systems' advantages and challenges. In fact, the number of patients by treatment group and a more consensual definition of ALF, may suggest less heterogeneity and more precise estimates, although only three included studies evaluated NBAL/BAL in ALF patients, evaluating only two systems (HepatAssist and MARS). The risk of SAEs was similar to SMT only, overall or by device category and, although patients with ACLF can present more comorbidities, the NBAL/BAL safety profile did not differ in comparison to ALF studies.

In line with another review (11), our results suggest that NBAL may have some impact on reducing overall mortality (pooled RR = 0.77; p = 0.076). We have identified RCTs from five NBAL systems—PE, MARS, Prometheus, DIALIVE, and Biologic-DT (discontinued)—showing inconsistent results. PE was shown to improve overall survival in one ACLF trial (32), and transplant-free survival in ALF (38, 39). MARS is U.S. Food and Drug Administration-approved for hepatotoxic ingestions and used off-label for hepatic encephalopathy and as a bridge to transplantation or recovery (47). Some RCTs showed significant improvements in hepatic encephalopathy in ACLF following MARS treatment suggesting its usefulness in these cases (25, 27). In a meta-analysis of individual patient data from three RCTs (25, 27, 28), MARS did not improve survival compared with SMT alone. This meta-analysis did show that age, Model for End-Stage Liver Disease (MELD) score, ACLF grade, number of MARS sessions received, and intensity of MARS therapy were

predictors of short-term survival (10-d) (13). These results are consistent with those from Prometheus RCT, which presented survival benefit only among more severe cases of ACLF (i.e., MELD > 30) (31). DIALIVE, a system with ultrafiltration of albumin and cytokines and a second filter to adsorb endotoxins and other inflammation agents, also did not show significant differences regarding 28-day mortality in ACLF patients even though improvement of organ failure markers was observed (24). These results inform the unmet need for further studies in a well-defined population with liver failure, to inform safety and consistency of injury biology and measurable reversible liver dysfunction (48).

While NBAL systems target the detoxifying function (7, 8, 49), BALs have the theoretical advantage of providing additional liver functions, namely metabolite synthesis, and biotransformation (8). In our review, we identified BAL systems with porcine hepatocytes (HepatAssist) or derived from human hepatoblastoma cell lines (ELAD). ELAD failed to demonstrate improved overall survival compared with SMT, with poorer clinical outcomes among older patients or those with higher MELD scores (26, 34, 50). However, HepatAssist showed promising results in patients with fulminant liver failure after adjusting for confounding factors (namely transplantation) (36). Clearly, ACLF grades 1 and 2 patient population group represents the largest liver failure therapy unmet need where improving ACLF before transplant or to avoid transplant is ethical, preferable and measurable, and would advance the optimal care paradigm (48).

Hepatocyte-based systems are still far from being an efficient solution, since isolation and preservation are expensive, and long-term support may require a large number of viable hepatocytes (42). In fact, hepatocytes lose liver-specific functions and the ability to replicate when isolated from their in vivo environment, both in terms of supporting cells (e.g., sinusoidal endothelial cells, Kupffer cells), liver tissue organization, and perfusion rates (51). On the other hand, despite the studies reporting constant blood flow rates, the detoxifying potency/activity at the beginning of perfusion is likely different than at the end of the perfusion, decreasing the efficacy of the devices over the time used. Hence, our meta-analysis suggests there is room for further development of NBAL/BAL systems, with careful definition of study population and subgroups, as well as optimization of perfusion time, and decision about albumin exchange. In fact, there are still some concerns on the reduction of albumin in patients with ALF and ACLF, which is not replaced in NBAL/BAL systems. The recent pilot study of Acute Physiology and Chronic Health Evaluation trial evaluated PE using albumin 5% as a replacement fluid and observed increased native albumin levels and improved albumin binding capacity, as well as improved circulatory, renal, cerebral, and liver function, and of systemic inflammatory response (52, 53). However, the single-arm design, the small sample size (n = 10) with heterogeneous procedures, and the reduced time of follow-up (1 mo) are pointed out as limitations on the validity of these results (52).

In this context, W-ECLP reappears as a promising system, with the expectation that, in the short-term, pig albumin could be as effective as human albumin at controlling biologic functions and binding toxins, in addition to other similarities in the structure and function of the hepatocyte supporting cells. Most W-ECLP systems involve using a porcine liver as a temporary support system for patients with liver failure waiting for transplantation. With this technique, the patient's blood is perfused through a liver removed from a pig and maintained ex vivo (10). During perfusion, the porcine liver provides essential liver functions (metabolism, detoxification, and protein synthesis), while removing harmful substances from the patient's blood, thus improving liver function and survival, as observed in most of the case reports eligible for this review. We analyzed six studies evaluating W-ECLP systems in adult patients and, interestingly, the studies reporting shorter perfusion durations seem to have worse outcomes, suggesting that either perfusion times were not consistently long enough to elicit a clinical benefit or that the pig liver suffered injury that prevented longer perfusion times. No relevant differences in liver function biomarkers were observed when using human livers not eligible for transplantation but selected for W-ECLP, or pig livers (42, 45). The transmission of porcine viruses to humans was evaluated of the study by Levy et al (46) included in our W-ECLP review, which results did not support these concerns and are in line with recent reports of ex vivo human livers rehabilitated through porcine cross-circulation (54). Although immunological changes in the porcine livers were observed, the deposition of IgM, IgG, and

complement varied across case studies. Furthermore, in vitro studies showed that serum from patients with liver failure caused less injury to pig liver endothelium than serum from healthy subjects and presented similar levels of xenoreactive antibodies (43). Tector et al (43) reported that the use of pig livers transgenic for CD55 and CD59 was a probable explanation for the weak anti-porcine IgG and IgM antibody deposits in the perfused livers. Recently, CRISPR (clustered regularly interspaced short palindromic repeats) technology was used to breed transgenic pigs (including knocking off three pig genes to prevent immediate immune rejection and inserting seven human genes involved in inflammation, immunity, and blood clotting) and significantly longer survival was reported when performing a kidney transplant to a monkey (55). Future studies could also address the combination of liver support systems with other organ support systems (e.g., sepsis columns) to treat multiple organ failure that frequently accompanies liver failure. In this context, the pig liver-Organox-decedent hepatic human donor perfusion experience is expected to provide insight on pig liver drug metabolism, pharmacologic human physiologic life support, and on the efficacy of porcine liver proteins such as pig albumin compared with human mercaptalbumin and coagulation proteins (56, 57).

Systematic reviews in this research area have important limitations. Studies evaluating NBAL/BAL systems presented considerable heterogeneity, namely regarding the reported outcomes and when they were assessed. Some studies considered only transplant-free survival, which is rarely the clinical objective when considering the use of these devices. Instead, examining and defining efficacy in these cases as a bridge to transplant and reversal of specific organ failure (e.g., hepatic encephalopathy) can provide more insight into the management of severe liver failure.

Although our meta-analyses included studies with different liver failure populations and different devices, we did not find significant differences in the subgroup analyses. The few differences in patients' demographics between ALF and ACLF studies are probably due to the different etiology of these conditions but the baseline characteristics of intervention and SMT groups were largely well-balanced. However, we cannot exclude that older studies may have considered different definitions of ACLF, which has been better defined in the last 10 years (53). Nevertheless, we found similar results in the sensitivity analysis considering only studies published after 2010.

In contrast to other meta-analyses that have combined different timepoints (besides assuming other non-randomized studies and smaller trials) (7, 11, 12), we minimized the survival bias associated with the different follow-up durations by choosing the most frequently reported and clinically relevant timepoint for mortality that could impair bridge to transplantation (i.e., 28–30 d) and by performing a subgroup analysis by timepoint of assessment for SAE outcome. Given the diversity of available literature, two separate searches were done, so that the best of each liver support system's respective literature base could be included. The review of W-ECLP systems is less robust than for NBAL/BAL devices, as available evidence consists only of case reports/series. Although all adult patients exposed to W-ECLP as reported by studies since 1990 were included in this review, the number is relatively small, and any interpretation should be made with caution. Nevertheless, these preliminary findings provide support and rationale for future studies and can guide the development of inclusion criteria and optimized perfusion duration. We also included the most recent W-ECLP cases (since 1990) and the most recent NBAL/BAL RCTs (since 2000) to reflect current practice as much as possible but, as we excluded NBAL/BAL trials with less than ten patients per group to avoid overestimation of effects in the meta-analysis, we may have omitted valuable data from small but potentially innovative trials.

CONCLUSIONS

The improvement in patient outcomes has not been consistently demonstrated with artificial liver support systems, despite significant research interest and efforts. However, the potential clinical relevancy of these systems in improving outcomes for liver failure patients supports the need for further research, notwithstanding their potential cost at both the development and eventual implementation phases. Well-designed multinational RCTs, with standard but center-adaptable treatment protocols, are required, with a correct number of an optimized and homogenous liver failure patient population, and quantitatively measured perfusion durability. Other studies on interspecies liver

physiology and the supporting cells' role are also important to a better understanding and design of liver support systems.

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