

REVIEW ARTICLE

Artificial liver support systemsRadhika Tandon*  and Saied Froghi*[†] *Guys Campus, King's College London, and [†]Department of HPB and Liver Transplantation, Royal Free Hospital, London, UK**Key words**

artificial, extracorporeal circulation, liver, transplant.

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Abstract

Artificial liver systems are used to bridge between transplantation or to allow a patient's liver to recover. They are used in patients with acute liver failure (ALF) and acute-on-chronic liver failure. There are five artificial systems currently in use: molecular adsorbent recirculating system (MARS), single-pass albumin dialysis (SPAD), Prometheus, selective plasma filtration therapy, and hemodiafiltration. The aim is to compare existing data on the efficiency of these devices. A literature search was conducted using online libraries. Inclusion criteria included randomized control trials or comparative human studies published after the year 2000. A systematic review was conducted for the five individual devices with a more detailed comparison of the biochemistry for the SPAD and MARS systems. Eighty-nine patients were involved in the review comparing SPAD and MARS. Results showed that there was an average reduction in bilirubin ($-53 \mu\text{mol/L}$ in MARS and $-50 \mu\text{mol/L}$ in SPAD), creatinine ($-19.5 \mu\text{mol/L}$ in MARS and $-7.5 \mu\text{mol/L}$ in SPAD), urea (-0.9 mmol/L in MARS and -0.75 mmol/L in SPAD), and gamma-glutamyl transferase ($-0.215 \mu\text{mol/L}\cdot\text{s}$ in MARS and $-0.295 \mu\text{mol/L}\cdot\text{s}$ in SPAD) in both SPAD and MARS. However, there was no significant difference between the changes in the two systems. This review demonstrated that both MARS and SPAD aid recovery of ALF. There is no difference between the efficiency of MARS and SPAD. Because of the limited data, there is a need for more randomized control trials. Evaluating cost and patient preference would aid in differentiating the systems.

Introduction

The liver is the largest and one of the most complex organs in the body.^{1,2} Its functions include glucose metabolism, immune system support, and detoxification.¹ Acute liver failure (ALF) is a rare but life-threatening illness.³ The leading causes are hepatitis A and E and drug-induced liver injury (which is responsible for approximately 50% of ALF cases in the United States).³ The term acute-on-chronic liver failure (ACLF) defined as an acute exacerbation of chronic liver damage, which is caused by the acute insult regardless of the presence or absence of cirrhosis.⁴ Liver transplantation is the only curative option for both ALF and ACLF, with both conditions having high morbidity and mortality.^{2,5} The success of liver transplantation has led to the number of potential recipients for liver transplant exceeding organ supply.⁶ In 2013, only 77% of patients on the European Union waiting list for liver transplant were successful in gaining a donor organ.²

Extracorporeal liver-assist devices allow support, as a "bridge," until a donor's liver becomes available or until the patients' liver can recover.⁷ There are two main types of device: artificial and bioartificial.² Artificial liver devices use nonliving components to detoxify the blood or plasma.² Removal uses physical or chemical gradients and adsorption.² The toxins and metabolic waste are mixed with albumin molecules then carried out of the blood.⁸ There are four central artificial systems currently in use: molecular adsorbent recirculating system (MARS), single-pass albumin dialysis (SPAD), fractionated plasma separation and adsorption system (Prometheus), and selective plasma filtration therapy

(SEPET).² Patients are eligible for these systems if they have ALF or ACLF (Table 1).²

In some countries, these systems are not approved. Therefore, other methods have had to be utilized to remove and exchange plasma components. One commonly used technique includes plasma exchange; however, this comes with many disadvantages such as hyponatremia and metabolic acidosis. It is now common to add hemodiafiltration to this treatment regime in the treatment of ACF to improve survival rates.^{9,10}

This study compares all five artificial liver systems, which has not been done previously. This review aims to compare data from existing literature directly, examine the devices use, and determine which device (focusing on SPAD or MARS) works more effectively.¹¹ This is important in terms of future treatments for ALF and ACLF and which device offers a better outcome.

Methods

Preliminary research. Preliminary literature searches were completed on PubMed and Ovid for each of the liver devices. Search criteria were "MARS" or "molecular adsorbent recirculating system" when studying the MARS device. Search criteria were "SPAD" or "single-pass albumin dialysis" when searching the SPAD device. To find studies regarding Prometheus, "Prometheus" or "fractionated plasma separation and adsorption system" or "FPSA" was searched. Studies describing

Table 1 Indications for Artificial Liver Support⁸

- ALF due to hepatitis A and B.
- ALF due to toxicity due to acetaminophen.
- Severe acute alcoholic hepatitis.
- Acute exacerbation of chronic liver disease, like a GI bleed, caused by another condition.
- Spontaneous bacterial peritonitis.
- Sepsis.
- Hepatorenal syndrome type 1 with sudden deterioration of liver function and acute renal failure.
- Hepatorenal syndrome type 2 with a slow deterioration of liver function. To bridge transplantation rather than treat liver failure
- If awaiting a liver transplant and complications such as hepatic encephalopathy or irreversible liver damage occur when there is a delay in procuring a suitable organ.
- Post liver transplant and primary nonfunction.
- Post liver transplant and delayed function of the graft.
- Intractable pruritus.

ALF, acute liver failure; GI, gastrointestinal.

hemodiafiltration were found using the criteria (“hemodiafiltration” OR “hemodiafiltration”) AND “liver”. For each of the preliminary searches, case studies and non-human studies were excluded. Articles from 2000–2019 were used.

These data were used to research about how each device works and its uses. Data were also used to provide pooled averages for biochemical changes to show the efficacy of the device.

Literary search. A further literature search for a comparison between SPAD and MARS was completed. A computer-based literary search was completed using the following bibliographic databases in February 2019: PubMed, Cochrane, Ovid, and Web of Science. Articles searched for were published from 2000 to 2019. The inclusion criteria were availability of the full text of the article, type of article was a comparison study or randomized control trial, and human studies only. The bibliographies of the recovered articles were reviewed to identify any other relevant papers.

Data extraction. In the first phase of the search, 60 974 articles were found. After the addition of inclusion and exclusion criteria, only 114 papers were remaining. After removing articles that did not fit the inclusion criteria, 17 articles were obtained. Further analysis and removal of duplicate articles resulted in two articles that adequately fit the inclusion criteria. A flow chart of the study selection process is depicted in Figure 1. The papers were reviewed, and data extracted by two independent reviewers (RT and SF). The following pieces of data were collected from each study: first author, year of publication, country, aim and type of study, participants, mean age of participants, male to female ratio of participants, APACHE score on arrival, treatment that the patient received (MARS or SPAD), hospital diagnosis, and outcome of study.

Outcomes. All outcomes were assessed after the maximum follow up (this was between 3 and 4 years, depending on the study). The following pieces of data from the study were used to assess outcome: average duration of each treatment, changes in bilirubin, creatinine, urea, and gamma-glutamyl transferase

(GGT) before and after treatment with SPAD or MARS. Hospital survival was assessed as the outcome of the patient. The average flow rate and albumin content used in SPAD and MARS were also compared with ensure comparability between studies. Safety of the patients was compared by assessing the hemodynamic support and transfusion rates each patient needed and also looking for any adverse effects during the study period. Hepatic encephalopathy was also assessed.

Methodological quality assessment. Two authors independently assessed the quality of the papers. The type of paper was examined for rating the quality of evidence.¹³ These were examined to determine any bias in the allocation sequence generation, blinding, completeness of outcome data, and outcome reporting. Missing data, internal data consistencies, randomization integrity, follow up, and censoring pattern assessed the quality of individual studies. Oxford Grades of Recommendations were used to assess the quality of evidence.¹⁴

Results

Molecular adsorbent recirculating system. The MARS system was first introduced by Stange *et al.* in the 1990s and is the most widely studied device.^{15,16} It involves two circuits: one has an albumin-impermeable high-flux dialyzer and the other secondary circuit is prefilled with albumin solution (Fig. 2).¹⁸ The albumin solution is circulated in a closed circuit, which is separated from the patients' blood by the high flux hemodialysis filter.⁹ The albumin is dialyzed using a standard 5–10% dialysis solution in continuous veno-venous hemodialysis over an albumin impermeable membrane.⁹ Albumin-bound toxins in the plasma pass on to the membrane-impregnated albumin and are picked up by the dialysate.¹⁹ Substances with a molecular weight of more than 50 kDa are not removed due to the membrane pore size.¹⁹

A significant challenge of MARS is its cost per patient compared with other treatments. It was suggested that if MARS was available more widely and the method was routinely used, it would become cheaper.¹⁷ MARS is usually well tolerated; however, the only consistent adverse effect is thrombocytopenia.¹⁹ This

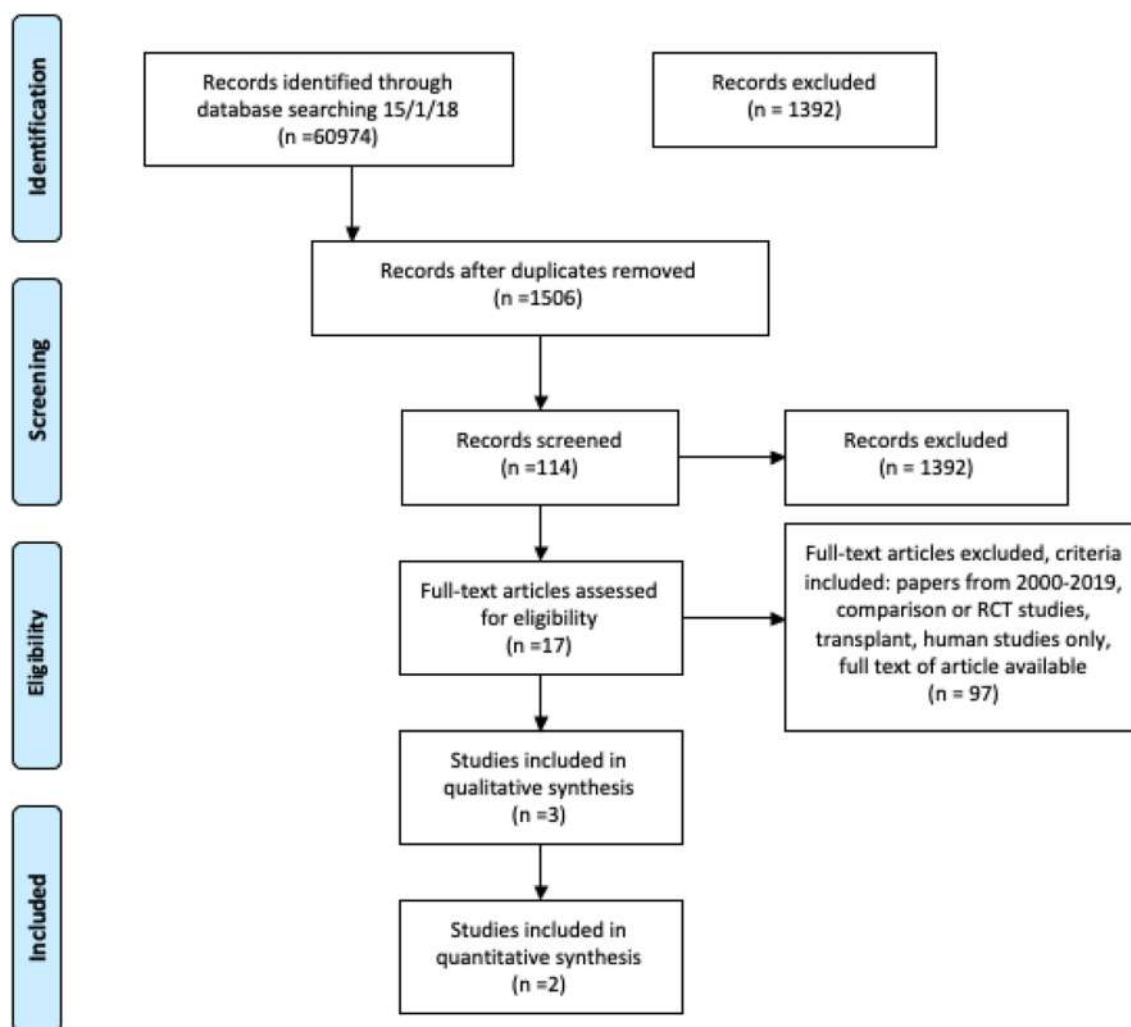


Figure 1 Flow chart of the literature search and study selection (adapted from PRISMA criteria).¹² RCT, randomized controlled trial. [Color figure can be viewed at wileyonlinelibrary.com]

suggests that it should be contraindicated in patients with disseminated intravascular coagulation or those with incipient disseminated intravascular coagulation.¹⁹

A total of eight papers that examined the use of MARS were found (Appendix A). These papers tested MARS on 459 patients. A study by Quintero Bernabeu *et al.* examined 11 pediatric patients and showed a significant decrease in blood toxins in patients with ALF.²⁰ This study infused heparin into the system for each patient, which was not commonly used in other studies. This paper highlights the length of time MARS was used for.²⁰ MARS was originally intended to be used for approximately 6–8 h; however, in this study, 18 of the cycles were over 8 h long.²⁰ This shows that MARS can also be used for varying periods of time without consequences to the patient.²⁰

A retrospective analysis with 101 patients was completed by Gerth *et al.*²¹ This study focused on different patient groups that would benefit from MARS.²¹ Unlike the study completed by Quintero Bernabeu *et al.*, this paper had an average treatment time of 360 min, and MARS was stopped once bilirubin had decreased

significantly.²¹ This contradicts the first study showing that although MARS can be used for a longer period of time, changes to biochemical values occur after a much shorter period of time.²¹ This study also showed that MARS does effectively reduce mortality but that the effect is temporary and deteriorates after discontinuing.²¹ The results showed that patients with a low ACLF grade also do not benefit from addition of MARS to standard medical treatment.²¹ Hepatic encephalopathy was reduced in 78.8% of patients (compared with 39.5% in standard medical treatment).

The third paper in the review tested 73 patients with ALF and graft dysfunction with a long follow-up period of 6.5 years.²² The median cumulative duration of therapy was 10 h; however, the paper did not detail each individual length of therapy.²² It showed that MARS had no advantages over standard medical therapy to 28-day mortality, but it did show that MARS causes significant decreases in bilirubin values.²²

Olin *et al.*²³ retrospectively studied 69 patients with a median treatment time of 27 h. As with the third study, the paper did not separate each individual length of therapy.²³ This study included

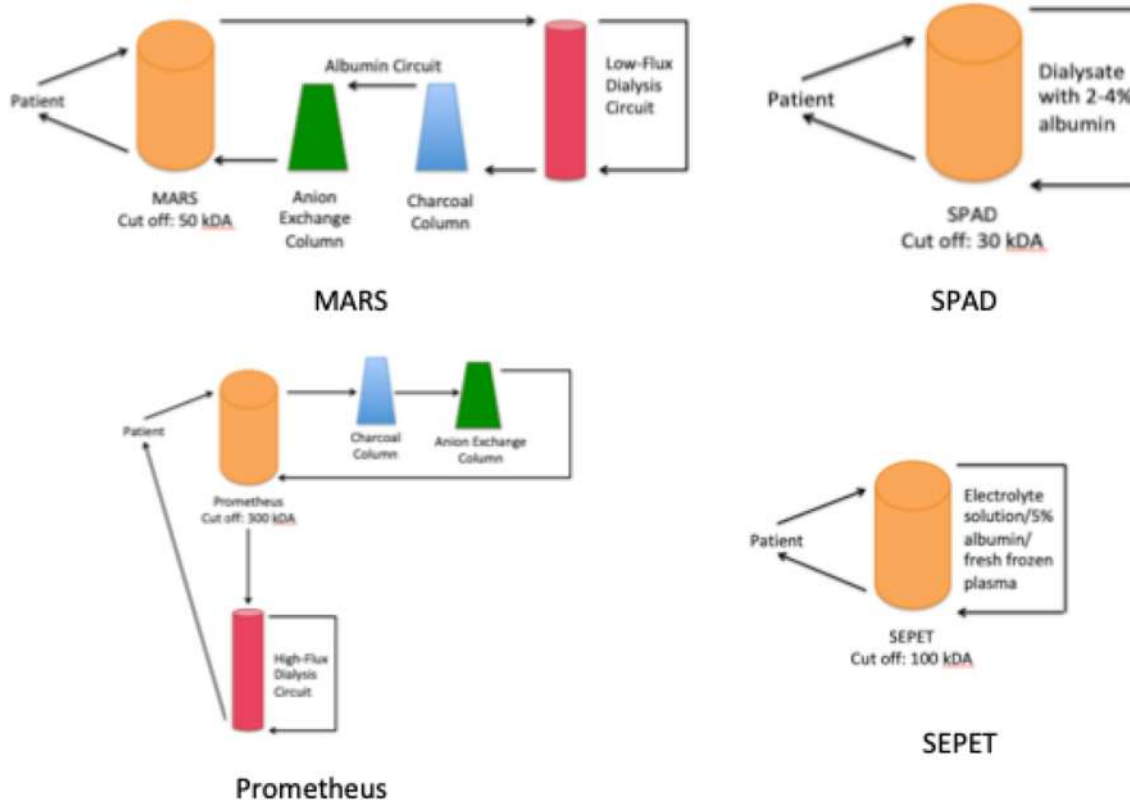


Figure 2 Schematic diagram showing how the MARS, SPAD, Prometheus, and SEPET systems run (adapted from Stadlbauer et al.).¹⁷ MARS, molecular adsorbent recirculating system; SEPET, selective plasma filtration therapy; SPAD, single-pass albumin dialysis. [Color figure can be viewed at wileyonlinelibrary.com]

both pediatric patients and adults (age ranging from 1 month to 70 years).²³ The study showed that MARS is a safe intervention in patients with ALF listed for liver transplantation.²³ It also suggested that MARS might not protect every patient from hyperammonemia, which is prevented by increasing filtration rates.²³

Lexmond *et al.*²⁴ observed 20 pediatric patients, which is the largest pediatric study included in this review. The mini-MARS system was used in children under 20 kg; however, it is not known whether this is as efficient as the original MARS system.²⁴ Heparin was also only used when activated clotting time was under 140 s.²⁴ Median treatment time was 8 h.²⁴ This study observed worse prognostic index scores for MARS treated patients and showed that MARS decreased ammonia and bilirubin regardless of whether the patients suffered from ALF or other Etiology.²⁴ This study also showed that hepatic encephalopathy improved in 30% of patients; however, in 45% of patients, the encephalopathy was worse.

A 3-year retrospective study was completed by Bourgoin *et al.*²⁵ This only studied six children and used the mini-MARS system in four of these patients.²⁵ The median duration for each session was 6 to 8 h.²⁵ This study showed that neurological status only improved in one patient and that MARS has limited to no efficacy on bilirubin level.²⁵ The study also showed that MARS had no effect on hepatic encephalopathy.

Donali *et al.*²⁶ carried out a prospective study with 269 MARS treatments on 64 patients. It grouped patients according to the aim: liver function recovery, liver transplants or on the waiting list for a liver transplant.²⁶ This study suggested that patients' prognostic factors were the biggest indicators on survival.²⁶ All MARS sessions lasted 5 h, and heparin was used first.²⁶ This study showed that MARS was safe and well tolerated.²⁶

Cisneros-Garza *et al.*²⁷ reviewed 79 MARS procedures over a period of 8 years. This was the only non-European study included in the review of MARS systems.²⁷ Anticoagulation was provided in some cases and a saline solution or heparin was administered at alternate hours during MARS treatment.²⁷ The best survival rate was in patients with hepatitis A virus and that MARS avoided transplantation in 37% of patients.²⁷ This study showed that hepatic encephalopathy had significantly improved from Grades 3 to 1 in six patients.

Seven of the papers reviewed reported a reduction in bilirubin levels after MARS treatment (on average reducing from 80.24 ± 68.28 to 76.50 ± 79.67 $\mu\text{mol/L}$). Five of the papers reported a reduction in ammonia after MARS treatment (on average reducing from 121.49 ± 55.59 to 83.40 ± 76.08 $\mu\text{mol/L}$). Creatinine was also reported in five papers. When averaging the figures for creatinine, there was a reduction from 59.73 ± 59.93 to 40.94 ± 55.31 $\mu\text{mol/L}$. Average survival across the papers was 65.98%.

Single-pass albumin dialysis. The SPAD system is newer and so is less well documented.¹⁹ The patients' blood flows through a circuit containing a high-flux hollow polysulfide hemodiafilter, identical to that used in the MARS system (Fig. 2).²⁸ The other side of the membrane is cleansed by a human albumin solution flowing in the opposite direction. This solution is then removed after passing through the filter.²⁸ This is a significant advantage of SPAD compared with MARS because a renal replacement therapy machine can be adapted to be used in SPAD, and more diluted albumin is used (4.4% rather than 20%).²⁸ This balances with the cost of not recirculating the dialysate, which MARS does do. Further studies need to be completed to explore this and further find limitations in SPAD.²⁸

Five papers were found that assessed the efficacy of SPAD (Appendix B). Ringe *et al.*²⁹ completed a retrospective review that included nine children between the ages of 2 and 15. This study took place over 6 years.²⁹ In this study, the extra corporeal circuit was prefilled with packed red blood cells, and veno-venous hemofiltration was also performed.²⁹ The study looked at blood pressure and proved that it remained stable during SPAD treatment.²⁹ This study showed that, in 66% of patients, hepatic encephalopathy was decreased by at least one degree.

Benyoub *et al.*³⁰ analyzed 14 patients retrospectively. This paper did not detail the ages of the patients observed but explained that the patients either had ALF or ACLF. Each SPAD treatment lasted 10 h.³⁰ Unlike the other studies using SPAD, all of the patients in this study received *n*-acetyl cysteine, antioxidant vitamins, terlipressin, or norepinephrine.³⁰ This concluded that there was a strong correlation between SPAD and the changes in bile acids and a weak but statistically significant decrease in bilirubin levels during SPAD.³⁰ The study also suggests that bile acids allow a more reliable prediction of the efficacy of the albumin dialysis.³⁰

Piechota *et al.*³¹ studied 101 patients over a period of 9 years. This retrospective study observed patients aged between 24 and 83 years old.³¹ It describes a preliminary phase, which involved a gradual increase in blood and plasma flow rates in the secondary circuit.³¹ Preliminary phases had not been used in other studies. Sodium citrate was used as an anticoagulant, and the SPAD treatment was completed in 6 to 10 h.³¹ There were high mortality rates recorded with SPAD in this study, but compared with the mortality of standard treatment (which was 83.03%), the mortality rate was still lower than this.³¹ This study showed that SPAD was effective at eliminating bilirubin and ammonia.³¹

Boonsrirat *et al.*³² completed 6-h-long SPAD treatments on 12 patients. All patients used had hyperbilirubinaemia.³² This study showed that SPAD causes no significant changes in ammonia levels.³² This study also only looked at survival after 15 days, which may change after a longer period of time.³² The study proved that SPAD was hemodynamically well tolerated in patients with very severe conditions and comorbid conditions.³² This study also claimed that SPAD was five times less expensive than MARS in the same situation. Unfortunately, the study did lack a comparative group and control group.³²

The final study in the SPAD analysis was also a retrospective study by Karvellas *et al.*³³ This study observed 13 patients whose average age was 38 years old.³³ It focused on patients who had had a paracetamol overdose and observed them over 3 years.³³ Unlike other studies, no anticoagulation was used.³³ A control was also completed with patients in the intensive care unit but not receiving

SPAD.³³ The study did not show any short-term clinical, physiological, or lab parameter improvement when SPAD was used and did not find an improvement in the encephalopathy grade.³³

A total of 149 patients were included in the analysis for SPAD treatment. One of the papers was pediatric, with an average age of 8.22 years old. The other four papers had an average age of 42.73 years old. All five papers reported bilirubin levels when using SPAD: three of these reported a decrease in bilirubin, and two reported an increase of 0.33 and 121 $\mu\text{mol/L}$ in bilirubin. Four papers also showed a reduction in ammonia. There was an average reduction in ammonia from 127.64 ± 147.21 to $95.86 \pm 69.16 \mu\text{mol/L}$. Four of the papers reported creatinine levels. Three of these showed a decrease in ammonia when using SPAD, and one showed a decrease of 25.5 $\mu\text{mol/L}$.

Prometheus. This system was first used in 1999 and has been used over 100 times.³⁴ Prometheus is similar to MARS however uses a membrane with a 250-kDa cut-off between circuits, which make the membrane permeable to albumin (Fig. 2).³⁴ This may be advantageous to toxin removal as many toxins in liver failure are still bound by albumin.³⁴ Prometheus is also preloaded with the patient's albumin rather than with exogenous albumin as with the MARS system.³⁴ This leads to a drop in patient's albumin levels; however, the consequences of this have not been fully explored.³⁴ A disadvantage of Prometheus is that it places the high flux dialyzer in the albumin circuit with the patient's bloodstream.³⁴ This raises the risk of clotting, and anticoagulation has been used to reduce this risk.³⁴

Ten papers were found that assessed the efficacy of Prometheus (Appendix C). The first study retrospectively examined the safety of Prometheus in 39 patients.³⁵ This study observed how the Prometheus system supported patients after cardiac and vascular surgery.³⁵ The average age of participants in the study was 59 years old.³⁵ This study used heparin as anticoagulation.³⁵ It showed no significant changes in albumin but a significant reduction in bilirubin.³⁵ It proved a reduction in liver parenchyma damage through decrease in aspartate transaminase and alanine aminotransferase levels.³⁵

Kribben *et al.*³⁶ completed a study with 145 patients. This was a prospective randomized multicenter trial.³⁶ Each patient had between 8 and 11 rounds of Prometheus for a minimum of 4 h.³⁶ As with other studies, it showed that serum bilirubin significantly decreased but not other parameters.³⁶ This study also showed no significant differences in survival between Prometheus and standard medical treatment.³⁶

Rifai *et al.*³⁷ observed 11 patients with ACLF and renal failure. Prometheus was used for 2 days for over 4 h.³⁷ Unlike other studies, patients were followed until discharge or death.³⁷ The study also used unfractionated heparin during treatment and showed that clotting of the tubing was a frequent problem if the patient had liver failure or bleeding problems because of restraints with too much heparin.³⁷ The study concluded that there was a significant decrease of laboratory parameters within 2 days; however, there was no improvement of the hepatic encephalopathy score.³⁷

Grodzicki *et al.*³⁸ completed 278 procedures in 114 patients with a median age of 33 years old. Each procedure lasted for approximately 6 h.³⁸ The study proved that Prometheus was useful for detoxification in patients with ALF by showing significant

reductions in all measured biochemical parameters.³⁸ The study also showed that Prometheus allowed adjusting for patients' body temperatures, which was not possible in other artificial liver systems.³⁸

Oppert *et al.*³⁹ retrospectively observed 23 patients. Each Prometheus session lasted from 5 to 6 h.³⁹ Unlike other papers, this study showed that the patients that benefitted most from the treatment had ALF or shock liver, and their underlying pathology was under control.³⁹

Rifai *et al.*⁴⁰ followed seven patients with various liver conditions and severe pruritus. These patients were only followed for 4 weeks.⁴⁰ Their mean age was 46 years old, and approximately, 71% were male.⁴⁰ The patients were treated with Prometheus three to five times for a total of 18 ± 3 h.⁴⁰

Santoro *et al.*⁴¹ observed 12 patients. These patients had severe hyperbilirubinemia, hyperkalemia, and hyperammonemia.⁴¹ Approximately, 340 sessions of Prometheus were completed in total.⁴¹ Unlike other studies, this paper chose broad inclusion criteria in order to evaluate the clinical application of Prometheus.⁴¹ This made it harder to draw conclusive results in terms of outcome and survival.⁴¹ The study proved that ammonia, bilirubin, and bile acids reduced in all types of patients after treatment.⁴¹

Skwarek *et al.* observed 13 patients while completing 29 procedures of Prometheus.⁴⁰ The mean duration of each treatment was 6.5 h.⁴² As with other papers, unfractionated heparin was used as anticoagulation.⁴² As well as significant decreases in albumin, the study also noticed normalization of sodium and pH after treatment.⁴²

Evenpeol *et al.*⁴³ studied nine patients with ACLF over a period of 2 years. This study showed that the rate and efficacy of removal of albumin binding toxins is related to both strength of albumin binding and saturation of adsorption columns.⁴³ Anticoagulation was completed with unfractionated heparin or regional citrate.⁴³ Twenty-four sessions of Prometheus were performed in total. Overall, this study showed that Prometheus is hemodynamically well tolerated.⁴³

Rifai *et al.*⁴⁴ studied 10 patients and showed that Prometheus is uncomplicated and safe. Similar to the study by Skwarek *et al.*,⁴⁴ this study also showed pH improved with Prometheus. Anticoagulation was unfractionated heparin that was administered as a bolus.⁴⁴ This study also found a significant increase in leukocytes but no other inflammatory markers, which has not been observed in other studies.⁴⁴ Hepatic encephalopathy score tended to improve slightly during Prometheus treatment without statistical significance.

The analysis of Prometheus included a total of 383 patients. There were no pediatric studies included in the analysis, and the average age of participants was 48.72 years old. All 10 papers reported a reduction in bilirubin levels. Ammonia was only reported in six papers of which all reported a reduction on average of $32.24 \mu\text{mol/L}$. Seven papers reported a decrease in the levels of creatinine with use of Prometheus. When averaging the figures for creatinine, there was a reduction from 34.43 ± 12.26 to $22.84 \pm 8.05 \mu\text{mol/L}$.

Selective plasma filtration therapy. The SEPET device is new and is a single-use cartridge that contains porous tubes made of biocompatible and hemocompatible material (Fig. 2).⁴⁵

The concept began after studies found that there was a loss of hepatic parenchyma and positive and negative regulators of hepatocyte parenchyma.⁴⁵ Substances with a molecular weight of up to 100 kDa can move through these tubes and across the porous wall to be discarded.⁴⁵ Electrolyte solution, human albumin solution, fresh frozen plasma, or a combination of the above is then used as a fluid replacement.⁴⁵ A significant advantage of SEPET is that a near-total exchange of albumin during therapy can be achieved.⁴⁶ This has been tested *in vitro* and in pigs, which have shown that it is safe and capable of extending survival time in treated animals.⁴⁶ A phase one trial has also shown that SEPET is safe. The Food and Drug Administration has approved phase two/three trials; however, they have not begun due to a lack of funding.⁴⁶

Because of a lack of data found in the preliminary literature search for SEPET, only a case study and animal study was found. A study completed by Rozga *et al.* showed that all treatments were well tolerated and life expectancy for the animals was significantly longer than the control group (31.5 ± 5.1 h vs 24.5 ± 5.5 h).⁴⁷ Ammonia values decreased significantly in the SEPET treatment group (379 ± 88 to 312 ± 54 mmol/L/L).⁴⁷ Bilirubin also decreased in the group that received SEPET (5283 ± 1676 to 3332 ± 1013 U/L).⁴⁷ Similar trends were shown in a case study by Nakae *et al.*⁴⁷ Bilirubin reduced from 23.5 ± 3.7 to 16.4 ± 2.5 mg/dL, creatinine reduced from 1.6 ± 0.4 to 1.3 ± 0.3 mg/dL, and no significant changes were found in the albumin level.⁴⁷ Life expectancy was not reported.⁴⁷

Hemodiafiltration. Hemodiafiltration has been used most frequently in Japan, where the MARS system is not yet approved.^{48,49} It works in addition to plasma exchange by removing substances causing hepatic encephalopathy as well as waste substances to be metabolized in the liver for excretion.⁵⁰ It also supplies biological substances such as blood coagulation factors.⁵¹ It is believed to have a greater capacity for blood purification and therefore support impaired liver function and the substances responsible for hepatic encephalopathy better than the MARS system.⁵² The main advantage is the reduction of cost of blood purification therapy in comparison with other artificial liver systems.⁵³ It also simplifies the setup of the dialysis monitor.⁵³

Eight studies fit the criteria and could be used to assess the efficacy of hemodiafiltration (Appendix D). The first paper was completed in 2019 by Nand *et al.*⁵⁴ This prospective study examined 30 patients and showed that the use of hemodiafiltration was effective. Patients were treated for 27.32 ± 1.58 h.⁵⁴ Hepatic encephalopathy, serum bicarbonate, urea, and creatinine levels improved significantly during the procedure. This study also showed that the most common complication from the treatment was filter clotting and metabolic acidosis improved with the hemodiafiltration.⁵⁴

Yonekawa *et al.*⁹ completed a study with nine patients and looked at the effect of hemodiafiltration with plasma exchange. Although this study had a small study group and did not examine the liver systems individually, it showed that hemodiafiltration was beneficial. It measured citrate levels, IL-6 and IL-18 rather than the more commonly used urea, creatinine, and ammonia. The study showed that there was lower citrate and IL-18 levels but not IL-6 levels.⁹

Li *et al.*⁵⁵ examined 19 patients with multiple organ dysfunction syndrome and liver failure. This study also did not examine hemodiafiltration individually but compared it alongside plasma exchange and hemoperfusion. The study showed an improvement in bilirubin as well as vital signs (heart rate and blood pressure) and ALT (alanine aminotransferase) levels. Unfortunately, this study also did not examine ammonia or creatinine levels. A total of 51 sessions were completed between 19 patients.⁵⁵ This study showed that when plasma exchange was combined with hemodiafiltration, it was more effective than when combined with hemoperfusion and all three treatments together were the most effective.⁵⁵

Nakae *et al.*¹⁰ studied the use of plasma exchange and hemodiafiltration in fulminant hepatitis. Bilirubin, citrate and IL-6 and IL-18 levels were compared before and after treatment. This study also had a small sample size of 10 patients and concluded that using both plasma exchange and hemodiafiltration were effective when used together to remove substances; however, it did not address the use of hemodiafiltration on its own.¹⁰

Abe *et al.*⁵⁶ examined hemodiafiltration with plasma exchange compared with plasma exchange alone. This study showed that sodium levels were not altered by either treatment but potassium, citrate, and calcium were decreased in all treatment arms. It showed that complications caused by plasma exchange were corrected by hemodiafiltration; however, the changes in calcium and citrate were insufficient. The study suggested altering the dialysate concentrations in the future to avoid these difficulties and that simply using plasma exchange with hemodiafiltrate was insufficient.⁵⁶

Yokoi *et al.* compared hemodiafiltration with plasma exchange in 90 patients with fulminant hepatitis.⁵¹ This retrospective cohort study compared four treatment methods (including hemodiafiltration alone). This study demonstrated that hemodiafiltration had a higher survival rate than plasma exchange. Ammonia was also effectively decreased.⁵¹ A total of 70.2% of patients had an improvement in hepatic encephalopathy grade.

The final study was completed in 2019 by Fujiwara *et al.*⁵³ and used 110 patients in Japan. This study analyzed recovery rates and found that there was a higher rate of recovery of consciousness in patients that had received hemodiafiltration than the current therapy (plasma exchange). This study also examined the types of hemodiafiltration and found that pre-dilution is superior to conventional hemodiafiltration. The survival benefit or individual plasma components such as ammonia or urea were not addressed.⁵³

A total of 279 patients were included in the analysis for hemodiafiltration treatment. No pediatric cases were included. The average age of patients was 51.58 years old. Unfortunately, there was a lack of data in the papers; none of the studies reported ammonia levels, and one paper reported a decrease in creatinine levels (by 3.04 $\mu\text{mol/L}$). Four of the papers reported a change in bilirubin on average of $17.19 \pm 15.26 \mu\text{mol/L}$.

Molecular adsorbent recirculating system versus single-pass albumin dialysis

Characteristics of included studies. A total of two articles that fully adhered to the inclusion and exclusion criteria

were selected. The publication years of the included studies ranged from 2000 to 2018. The articles compared SMAD and MARS in the treatment of liver failure. A total of 89 patients with ALF or ACLF were involved in this review, including 56 male and 33 female patients. The median age of all patients was 53 years old. Thirty-three patients received only MARS: 12 received only SPAD, and 44 received both MARS and SPAD during the study. There were no control groups; the patients either received MARS, SPAD, or both treatments in succession. The characteristics and methodology quality of the included studies are summarized in Tables 2 and 3.

The study by Kortgen *et al.*²⁸ compared both systems in 57 patients prospectively. One hundred sixty-three treatments of MARS or SPAD were completed: 126 of these were with MARS and 37 were with SPAD. The mean duration of a MARS treatment was 10.9 h (± 4.48 h). The mean duration of each SPAD treatment was 5.5 h (± 0.71 h). Sponholz compared both MARS and SPAD in a retrospective study. The mean durations were 8.00 h (± 0.28 h) for MARS and 7.15 h (± 0.22 h) for SPAD treatments.

Outcome. Outcomes were measured using overall survival throughout the study period. Survival for patients that were given MARS was 42.42%. A total of 41.66% of patients given SPAD survived the study period. A total of 51.51% of patients that received both MARS and SPAD survived.

Serum bilirubin. Both trials produced data on changes to serum bilirubin levels. All patients had a significant reduction in serum total bilirubin levels. All *P* values were significant in each of the studies. In the trial by Kortgen *et al.*, *P* = 0.001 in MARS and *P* = 0.035 in SPAD. In the trial by Sponholz *et al.*, *P* = 0.001 for both MARS and SPAD. The average drop in bilirubin across both studies for MARS was $-53 \mu\text{mol/L}$ and for SPAD was $-50 \mu\text{mol/L}$. There was no significant difference between the devices.

Creatinine. The studies showed an average reduction of creatinine in MARS of $19.5 \mu\text{mol/L}$ and an average reduction of creatinine in SPAD of $7.5 \mu\text{mol/L}$. The *P* values were significant for MARS (*P* = 0.001 in the trial by Kortgen *et al.* and *P* < 0.001 in the trial by Sponholz) but not for SPAD (*P* = not significant in the trial by Kortgen and *P* = 0.314 in the trial by Sponholz). Although the change in creatinine was not significant for SPAD, there was no significant difference between the changes in creatinine for SPAD and MARS.

Urea. After treatment with MARS, urea reduced on average by 0.9 mmol/L. After treatment with SPAD, urea on average reduced by 0.8 mmol/L. However, the reduction in urea values used was only significant in one of the studies included in this review. There was no significant difference between the two devices (SPAD and MARS).

Gamma-glutamyl transferase. Gamma-glutamyl transferase reduced in all patients. On average, in patients receiving MARS, the reduction was $0.215 \mu\text{mol/L}\cdot\text{s}$. Whereas, in patients receiving SPAD, this reduction was $0.295 \mu\text{mol/L}\cdot\text{s}$. These values

Table 2 Summary of the characteristics and methodology of the included studies

First author	Date of study	Country	Aim of the study	Number of participants (and which treatment they received)	Mean (SD) age of participants (years old)	Male/Female ratio	APACHE score on arrival (SD)	Hospital diagnosis on arrival (number of participants)	Outcome of the study
Kortgen	2009	Germany	Retrospective analysis of SPAD and MARS in the treatment of ALF or ACLF.	57 (33 on MARS, 12 on SPAD and 12 on both)	50 ± 18.5	38/19	22 ± 8.1	Primary liver disease: 42 Other abdominal diseases: 7 Cardiac disease: 5 Sepsis: 1 Other: 2	Equal efficacy of SPAD and MARS
Sponholz	2016	Germany	Prospective comparison of SPAD and MARS in patients with liver failure.	32 patients with 69 crossover cycles of both SPAD and MARS	56.5 ± 4.04	18/14	21 ± 6.8	Acute on chronic liver failure: 18 Acute liver failure: 9 Liver graft failure: 5	Both SPAD and MARS are safe for artificial liver support

ALF, acute liver failure; ACLF, acute-on-chronic liver failure; MARS, molecular adsorbent recirculating system; SPAD, single-pass albumin dialysis.

Table 3 Summary of the results of the included studies

First author of study	Duration of treatment (SD) (h)		Change in bilirubin (μmol/L) (mean ± SD)		Change in GGT (μmol/L-s) (mean ± SD)		Change in creatinine (μmol/L) (mean ± SD)		Change in urea (mmol/L) (mean ± SD)	
	MARS	SPAD	MARS	SPAD	MARS	SPAD	MARS	SPAD	MARS	SPAD
Kortgen	10.9 ± 4.48	5.5 ± 0.71 h	-38 ± 66.5 (<i>P</i> = 0.001)	-41 ± 111.2 (<i>P</i> = 0.035)	-0.26 ± 1.009 (<i>P</i> = 0.009)	-0.46 ± 1.161 (<i>P</i> = 0.031)	-15 ± 38.5 (<i>P</i> = 0.001)	-13 ± 91.5 (<i>P</i> = not significant)	-0.9 ± 3.86 (<i>P</i> = not significant)	-1.4 ± 8.02 (<i>P</i> = not significant)
Sponholz	8 ± 0.28	7.15 ± 0.22	-68 ± 21.37 (<i>P</i> = 0.001)	-59 ± 13.86 (<i>P</i> = 0.001)	-0.17 ± 0.23 (<i>P</i> = 0.019)	-0.13 ± 0.20 (<i>P</i> > 0.05)	-24 ± 11.11 (<i>P</i> = 0.001)	-2 ± 4.62 (<i>P</i> = 0.314)	-0.9 ± 0.57 (<i>P</i> = 0.024)	-0.1 ± 0.53 (<i>P</i> = 0.523)

GGT, gamma-glutamyl transferase; MARS, molecular adsorbent recirculating system; SPAD, single-pass albumin dialysis.

were statistically significant, and there was no significant difference between SPAD and MARS.

Safety. One of the studies had no adverse effects on any patients. Hemodynamic support and the need for transfusion were not different in either system (MARS and SPAD). This study reported that transfusion of red blood cells in MARS was 1 ± 1.0 and in SPAD was 1 ± 1.1 . Fresh frozen plasma transfusions were 2 ± 2.8 in MARS and 1 ± 2.9 in SPAD. Transfusion of platelet concentrates was 0 ± 1.4 and 0 ± 0.7 . Hepatic encephalopathy was not assessed in this study, as there was no standardized protocol to document the degree of hepatic encephalopathy in the patient data management system files.

The second study did not comment on adverse effects.⁵⁷ This study demonstrated that there were no any differences between the hemodynamic requirements between the systems. The mean of all transfusion requirements are as follows: for erythrocytes 1, for fresh frozen plasma, there was a more considerable variation between the studies from 2 to 0. Platelet concentration was 0 for all treatments, which was the same as the other study. Hepatic encephalopathy, however, was assessed in the patients, and there were no changes after completion of one crossover cycle.

Discussion

Current evidence proves the efficacy of both MARS and SPAD in the context of ALF and ACLF. An *in vitro* study by Sauer *et al.* shows no significant differences between SPAD and MARS other than that SPAD induces a significantly higher reduction in bilirubin levels than MARS. However, this has not been shown in human studies.¹⁵ *In vitro* studies have also shown that SPAD has a similar or higher detoxifying capacity than MARS.¹⁶ Unfortunately, there are not many studies that compare both MARS and SPAD directly. In randomized control trials for MARS, improvements in the values of creatinine and bilirubin have been demonstrated.¹⁵ This is further backed by the RELIEF trial

showing a reduction in bilirubin and improvement in hepatic encephalopathy.¹⁵ There has also been proven benefits to the sequelae of ALF patients treated with MARS, showing significant improvement in encephalopathy, a reduction of cerebral edema and intracranial pressure.¹⁶ The newer indications such as pruritus have not been well documented. There is only a case of resolution of pruritus after MARS in the literature. Reported use of MARS in Wilson's disease in ALF with successful bridging to transplantation have also been documented.¹⁶

Single-pass albumin dialysis is a much newer device and so has had much fewer studies reported on it. For this reason, there are even fewer studies that compare both SPAD and MARS. It is efficient and can reverse hepatorenal syndrome in many case studies.¹⁶ The primary clinical use of SPAD that has been published is in Wilson's disease.⁵⁸ The study concluded that SPAD was efficient in clearing both bilirubin and copper.¹² The main issue with current studies is the lack of large randomized controlled trials that compare both SPAD and MARS. Current research proves the safety of the individual treatments and proves that they both work efficiently; however, it does not show which one is better to use and if the diagnosis of the patient affects the outcome.

The results of the preliminary searches showed that more large randomized control trials are needed for all five devices, especially with SEPET. The patients used to compare the devices in the studies had similar characteristics, and this showed that all devices are efficient and reduce biochemical values (Fig. 3). MARS was shown to have the highest survival rate (65.98%), followed by Prometheus and SPAD (Fig. 4). Prometheus was shown to have the most substantial effect on biochemical values (Fig. 5). MARS was also the only device that reduced bilirubin ($-53 \mu\text{mol/L}$, $P = 0.001$), creatinine ($-19.5 \mu\text{mol/L}$, $P = 0.001$), and ammonia in all studies. Hemodiafiltration was shown to be an effective method of treatment, with parameters normalizing. Unfortunately, because of the lack of studies using similar parameters to the other artificial liver system and testing the treatment without plasma exchange, it is difficult to thoroughly analyze and compare.

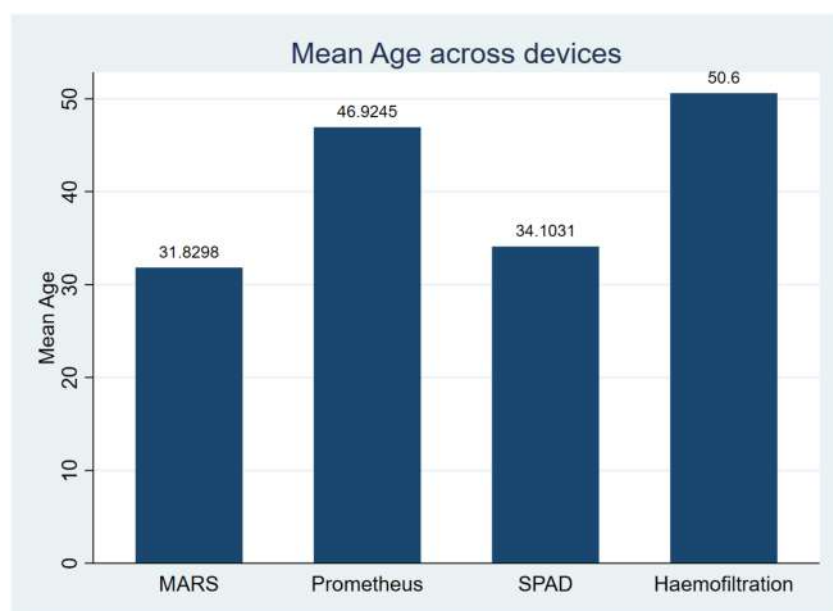


Figure 3 Mean ages of the participants used in the studies of hemodiafiltration, MARS, Prometheus, and SPAD. MARS, molecular adsorbent recirculating system; SPAD, single-pass albumin dialysis. [Color figure can be viewed at wileyonlinelibrary.com]

Figure 4 Average survival rates for hemodiafiltration, MARS, Prometheus, and SPAD artificial liver systems. MARS, molecular adsorbent recirculating system; SPAD, single-pass albumin dialysis. ■, MARS; ■, Prometheus; ■, SPAD; ■, hemodiafiltration. [Color figure can be viewed at wileyonlinelibrary.com]

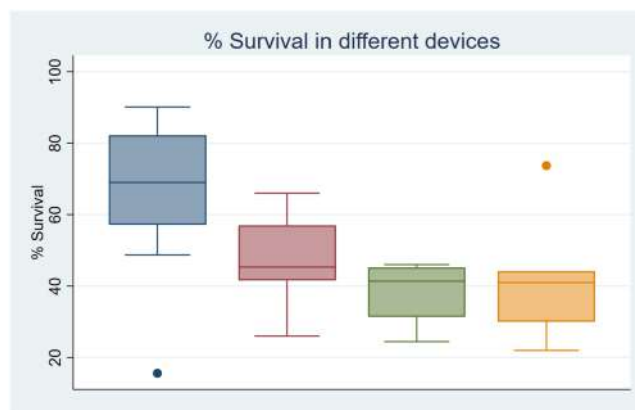
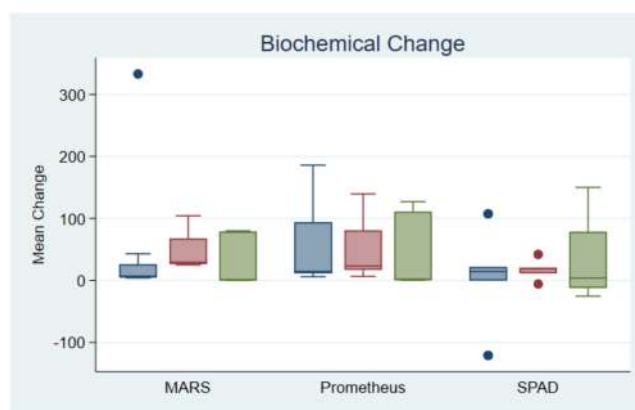


Figure 5 Summary of the biochemical changes in the MARS, Prometheus, and SPAD artificial liver systems. MARS, molecular adsorbent recirculating system; SPAD, single-pass albumin dialysis. ■, Bilirubin; ■, Creatinine; ■, Ammonia. [Color figure can be viewed at wileyonlinelibrary.com]



Both studies used in the review of SPAD and MARS were comparable in the type of study and aim. The studies have comparable flow rates and lengths of treatment times. The study proves that survival for all systems is similar. Both studies prove that the SPAD and MARS systems are safe and have similar transfusion requirements, which are low. Bilirubin is used as a prognostic in a critical care setting, so it is an important outcome to measure.⁵⁹ In both devices, there was no significant difference between the reductions in bilirubin levels; however, the changes in bilirubin itself were significant. This would follow the hypothesis that both MARS and SPAD can be used to treat ALF and ACLF. As shown in previous studies, it is unclear which system is better to use. This result differs from the *in vitro* study completed. This can be explained by the fact that human participants will react differently to MARS and SPAD. Similar to bilirubin, the changes in GGT shown by this review are significant, showing a reduction in mortality and a beneficial effect of both SPAD and MARS. In relation to this, there is not a significant difference between the two systems. This shows that while neither of the systems are better in reducing GGT, which has not been shown in previous studies, both SPAD and MARS produce a reduction in creatinine and urea. Results in SPAD are not significant, but in MARS, they are. The reduction in urea after both systems is not statistically significant; however, this could be due to the wide variety of functions of both urea and creatinine.

Limitations of this study include the lack of randomized control trials in the subject area. There is also a small patient population and an uneven distribution of each study arm. There are very few patients treated with SPAD that have been studied, which makes it hard to see the real association between SPAD and MARS. A disadvantage also includes the lack of comment on adverse effects in one of the studies, which does not allow full comparison. It is also important to identify whether the studies affect hepatic encephalopathy, which has not been fully explored.

Future studies would need to include a more extensive comparison of all systems, which would also incorporate aspects of cost and patient preference. The effectiveness of the devices also needs to be more thoroughly compared in the future. As more studies are completely between the systems, they will become safer to use. Further studies are needed to focus on and assess the optimum flow rates of each system. To show the optimal artificial liver device, testing against other bioartificial, artificial or hybrid liver systems, for example, AMC-Prometheus and SEPET should also be completed.² A new artificial support system that is evolving is the UCL-ARSeNEL (University College London albumin replacement system encompassing novel endotoxin ligation).⁵⁹ This separates plasma with a plasma filter and then replaces albumin and endotoxin ligation.⁵⁹ There are also systems being developed which focus on adsorbents.²⁴ By varying their pore and particle size biocompatibility could be improved.²⁵ A Japanese national

study used a combination of plasma exchange, hemodiafiltration, and an infusion of FFP, which restored consciousness in 53% of patients.⁵² This shows it is also important to examine combinations of treatments to find optimal treatments.

In conclusion, this narrative review compares the currently available artificial liver systems and proved that both MARS and SPAD are efficient at treating ALF and ACLF. They both led to a decrease in serum bilirubin (on average by 51.5 $\mu\text{mol/L}$), GGT (on average by 25.5 $\mu\text{mol/L}$), serum creatinine (on average by 13.5 $\mu\text{mol/L}$), and urea (on average by 0.83 mmol/L). However, the difference between MARS and SPAD reductions was not significant. For this reason, it is difficult to differentiate between the two systems apart from evaluating the cost and patient preference. Comparison between SPAD and MARS is made difficult by the lack of extensive number of studies, thus making reliable conclusion difficult. There is a need for more large randomized control trials and a large trial comparing all four systems.

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APPENDIX A

Table A1 Studies that compare the biochemical values of patients on MARS

First author	Quintero Bernabeu	Gerth	Gerth	Olin	Lexmond	Bourgoin	Donati	Cisneros-Garza
Date of study	2017	2017	2017	2014	2015	2013	2013	2014
Aim of study	Application of MARS in pediatrics.	Retrospective analysis of ACOCLF patients receiving either standard care or MARS.	Effects of MARS compared to SMT in patients with acute liver injury and graft dysfunction.	Utility of MARS.	Use of MARS in children listed for high urgency liver transplantation.	Response of children using MARS.	Use of MARS in 64 patients.	Effect of MARS on patients with ALF and ACOCLF in Mexico
Number of participants	11	101	73	82	52	6	64	70
Mean age of participants (years)	3.73	53.1	47.55	43	7.1	5.4	54.41	40.35
Change in bilirubin ($\mu\text{mol/L}$) (mean)	7.66	4.04	4.2	43.07	333	5	9.6	6.02
Change in ammonia ($\mu\text{mol/L}$) (mean)	104.25	Not available in paper	Not available in paper	27.52	Not available in paper	31	25	Not available in paper
Change in creatinine ($\mu\text{mol/L}$) (mean)	1.37	0.18	0.1	78.91	80	Not available in paper	Not available in paper	0.3
Survival rate (%)	90.1	82.2	78.1	87	69	57.14	15.6	48.7

ALF, acute liver failure; ACOCLF, acute-on-chronic liver failure; MARS, molecular adsorbent recirculating system; SPAD, single-pass albumin dialysis.

APPENDIX B

Table B1 Studies that compare the biochemical values of patients on SPAD

First author	Ring	Benyoub	Piechota	Boonsirrat	Karvellas
Date of study	2011	2011	2015	2009	2009
Aim of study	Experience of SPAD in children with ALF.	Measure the changes in bilirubin and bile acids induced by SPAD.	Evaluate the use of extracorporeal liver support in patients with severe liver dysfunction.	Efficacy of bilirubin reduction and safety of SPAD.	Changes in lab parameters by SPAD.
Number of participants	9	14	101	12	13
Mean age of participants (years)	8.22	Not available in paper	47.89	42.3	38
Change in bilirubin ($\mu\text{mol/L}$) (mean)	14.4	107.38	-0.33	22	-121
Change in ammonia ($\mu\text{mol/L}$) (mean)	19.6	-5.84	42.03	11.3	20
Change in creatinine ($\mu\text{mol/L}$) (mean)	Not available in paper	6.83	0.93	-25.5	150
Survival rate (%)	44.44	92.86	24.44	16.7	46

ALF, acute liver failure; SPAD, single-pass albumin dialysis.

APPENDIX C

Table C1 Studies that compare biochemical values of patients on Prometheus

First author	Komardina	Kribben	Rifai	Grodzicki	Oppert	Rifai	Santoro	Skwarek	Evenepoel	Rifai
Date of study	2017	2012	2003	2009	2009	2006	2006	2006	2005	2005
Aim of study	Assess the safety and efficacy of extracorporeal liver support in patients after cardiac surgery.	Survival of patients with AOCLEF treated with FPSA.	Safety, adsorber clinical efficacy and Prometheus.	Results of FPSA in ALF on patients with liver failure.	Effect of FPSA on patients with pruritus.	Effect of Prometheus on pruritus.	Use of Prometheus in 12 patients.	Use of FPSA in patients with ALF.	Removal capacity during a single 6 h treatment of Prometheus.	Treatment of Prometheus on patients with hepatorenal syndrome.
Number of participants	39	145	11	114	23	7	12	13	9	10
Mean age of participants (years)	59	50	52.27	33	52	46	45.2	Not available in paper	49	52
Change in bilirubin ($\mu\text{mol/L}$) (mean)	63	6	94	12.72	16.23	186	11.4	8.56	12.1	119
Change in ammonia ($\mu\text{mol/L}$) (mean)	Not available in paper	Not available in paper	18	139.5	Not available in paper	Not available in paper	28.4	80.9	6.4	17
Change in creatinine ($\mu\text{mol/L}$) (mean)	32	0.3	111	1.2	Not available in paper	Not available in paper	0.88	Not available in paper	1.2	127
Survival rate (%)	23	66	36	53.8	26	Not available in paper	41.6	57	78%	Not available in paper

ALF, acute liver failure; AOCLEF, acute-on-chronic liver failure; FPSA, fractionated plasma separation and adsorption.

APPENDIX D

Table D1 Studies that compare biochemical values of patients on hemodiafiltration

First author	Nand	Yonekawa	Li	Nakae	Abe	Yokoi	Fujiwara
Date of study	2019	2005	2014	2004	2004	2008	2019
Aim of study	Evaluate the roles of two different models of renal replacement therapies in patients with hepatic failure and hepatorenal syndrome.	Assess the effect of plasma exchange versus continuous hemodiafiltration in postoperative liver failure.	Assess the effect of various combined blood purification techniques in patients with non-viral acute liver failure complicated by MODS	Investigating the effectiveness of the series-parallel method for blood purification.	The impact of PE alone and in combination with HD and the problems related to its use.	Comparison of high flow dialysate hemodiafiltration with conventional ALS techniques.	Investigation of various ALS systems for fulminant hepatitis.
Number of participants	30	9	19	10	11	90	110
Mean age of participants (years)	Not available in paper	65	43.7	57	56.1	40.6	46.7
Change in bilirubin ($\mu\text{mol/L}$) (mean)	11.42	10.3	34.91	7	Not available in paper	Not available in paper	Not available in paper
Change in ammonia ($\mu\text{mol/L}$) (mean)	Not available in paper	Not available in paper	Not available in paper	Not available in paper	Not available in paper	Not available in paper	Not available in paper
Change in creatinine ($\mu\text{mol/L}$) (mean)	3.04	Not available in paper	Not available in paper	Not available in paper	Not available in paper	Not available in paper	Not available in paper
Survival rate (%)	30	22	73.7	10	Not available in paper	44.2	40