Chapter

Liver Assist Devices for Liver Failure

Amrendra Kumar Mandal, Pavani Garlapati, Benjamin Tiongson and Vijay Gayam

Abstract

Historically, mortality rates for liver failure have been high, regardless of the type. With new advancements in liver transplantation (LTx), 1-year survival rates have improved up to 95% in most recent estimates. While some patients may live past the critical period, the majority of patients do not survive the interval period for awaiting LTx or liver regeneration. The function of the liver to detoxify and correct several biochemical parameters has been achieved to some extent through artificial liver support technology, although constant innovations are still being developed for the most optimal liver support device. The complex function of the liver makes it challenging since it does not only detoxify toxic by-products but also participates in numerous other synthetic and metabolic functions of the body. Liver support systems are divided into an artificial liver assist device (ALD) and a bioartificial liver assist device (BLD). ALDs include molecular adsorbent recirculating system (MARS), Prometheus, single-pass albumin dialysis, and selective plasma filtration therapy. These devices work as a blood purification system of the liver. On the other hand, BLD has hepatic cell lines incorporated in its equipment, which aims to function as a complex biological liver system providing support to its biochemical processes. Several clinical and randomized trials have conflicting results on the survival of the patients with acute liver failure (ALF), and the ideal liver support system still seems a far-off goal.

Keywords: liver failure, liver assist devices, bioartificial liver assist device, artificial liver assist device

1. Background

In the last decade, liver-related deaths have been steadily increasing. In 2016, it was responsible for more than one million deaths across the world [1]. ALF is defined as a rapid onset deterioration of liver function with coagulopathy and onset of encephalopathy of a previously healthy individual. It can be further classified into hyper-acute, acute, and sub-acute according to the O'Grady system of classification. The clinical manifestation includes jaundice, encephalopathy, and hematemesis or melena; however, unlike chronic liver disease, ascites and portal hypertension are rarely seen. The common etiologies include acute viral hepatitis, drug-induced liver injury, and ischemic hepatocellular injury. High mortality rates are associated with ALF [2]. Supportive therapy options are limited in the interim

between the development of ALF until liver function improves/or the patient undergoes liver LTx. Due to limited organ availability for patients waiting for LTx, and the rapid deterioration of a patient with ALF, the mortality rate approaches approximately 50% [3, 4].

Numerous studies are ongoing in an attempt to delay or prevent the need for LTx in patients with ALF. Artificial hepatic assist devices, auxiliary liver transplantation, a liver dialysis system, and xenotransplantation are the most sought-after therapeutic options. Several liver assist devices (LAD) have been manufactured since the 1990s on the pathophysiological basis of albumin dialysis, the best-known being the following: the molecular adsorbent recirculating system (MARS), single-pass albumin dialysis system (SPAD), and the fractionated plasma separation and adsorption system –FPSA (Prometheus). These systems remove the albumin-bound toxins that accumulate in liver failure. Older techniques previously were not able to remove these toxins and maybe the reason for the ineffectiveness of traditionally designed devices. The knowledge gained from these provided a platform for a better understanding of newer LADs, to perform the liver's functions more effectively. LADs facilitate the removal of water-soluble substances, such as ammonia, urea, and other smaller proteins, such as some cytokines, by standard dialysis [3]. Removal of these cytokines and other identifiable inducers of hepatic encephalopathy (HE), such as amino acids (e.g., tryptophan or glutamine), reduces the grade of HE and consequently reduces complications of liver failure [5]. Furthermore, they function to remove conjugated or unconjugated bilirubin, protoporphyrin, bile acids, glycoside derivatives, phenols, short- and medium-chain fatty acids, such as octanoate, or heterocyclic organic compounds. In one study, removal of plasmatic nitric oxide (NO) and some pro-inflammatory and anti-inflammatory cytokines lead to the improvement of clinical conditions of HE, renal and respiratory function, and hemodynamic derangement and subsequent sequential organ failure [6].

LAD designed to treat patients with ALF are classified into two main categories: non-cell-based systems, including plasmapheresis, plasma exchange, albumin dialysis, and charcoal-based hemadsorption, and systems that incorporate hepatic tissue (bioartificial liver support systems) [7, 8].

In the last decade, a significant shift in the development of these devices has emerged. The utility and efficacy of these new LADs are currently being evaluated in the clinical setting.

1.1 Types of liver support systems

Liver support systems are divided broadly into two categories: biological and mechanical. Artificial or mechanical liver support consists of artificial and bioartificial systems. Two artificial systems, the MARS, and the SPAD, clear selected toxins; however, they provide no synthetic support, nor do they improve survival in a randomized clinical trial (RCT) [9].

Biological systems combine the functional potential of hepatocyte incorporation with that of hemodialysis, enabling non-invasive, continuous treatment for patients with ALF. Regardless of their safety and cost-effectiveness, they do not improve portal hypertension or portosystemic shunting [9].

1.2 Artificial liver support devices

1.2.1 Molecular adsorbent recirculating system (MARS)

MARS was developed in 1990 and is the most widely published and clinically used artificial liver support system (**Figure 1**). The method is based on two basic

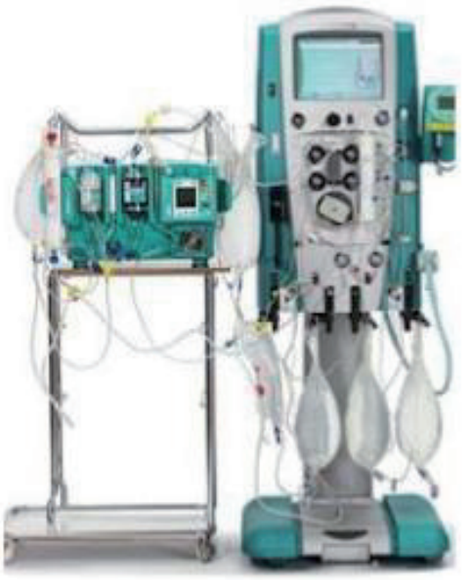

Figure 1.
Molecular adsorption recirculation system (MARS). Adapted from https://www.slideshare.net/tyfngnc/salon-a-17-kasim-2011-1410-1430-ender-egedik.

principles: protein-binding affinity and solute movement, which acts along the concentration gradient [10]. The combination of conventional dialysis against an albumin dialysate is utilized, followed by a traditional procedure of dialysis to remove the toxins from the dialysate [11]. It is composed of a blood circuit, an albumin circuit (containing 60 ml of 20% human albumin, charcoal column, and an anion exchange column with cholestyramine), and a traditional "renal" dialysate circuit as shown in **Figures 2–3**. Blood is passed through an albumin-incorporated high-flux dialysis membrane into which hydrophobic water-soluble and protein-bound toxins are released. The removal of toxins eventually takes place through the diffusion process, which depends on the free toxin level (mainly affected by the molar ratio of a toxin to albumin). The albumin dialysate is then recycled and is able to accept further toxins until both columns are saturated, eliminating the need for continuous infusion of albumin.

MARS can also eliminate cytokines and modify the inflammatory response involved in liver failure. Cytokines have been implicated in the development of HE, systemic inflammatory response syndrome (SIRS), vasodilation, and multiple organ failure. These proteins mediate hepatic inflammation, cholestasis, and liver cell necrosis and apoptosis [12]. Furthermore, studies have shown significant removal of some pro-inflammatory cytokines when using MARS, such as TNF-α, interleukin-6, and interleukin-1 β, and anti-inflammatory cytokines, such as interleukin-10 [13]. However, other studies were unable to demonstrate an effective change in the plasma cytokine concentration in patients with liver failure, possibly due to the high rate of its production [14]. Donati et al. showed 269 patients treated with MARS with no effect on cytokine plasma levels but a significant rise in hepatic growth factor concentration (enhances liver regeneration) [15]. In another study, Dominik et al. demonstrated some beneficial results in an in vitro study, where MARS improved the elimination of some cytokines with more extensive pore membranes, which could be attributed to optimizing the cytokine plasma profile of patients [16]. Ultimately, the precise roles of different cytokines in the pathophysiology of liver failure and the influence of MARS on cytokine profiles are yet to be understood and could be an exciting topic for further research.

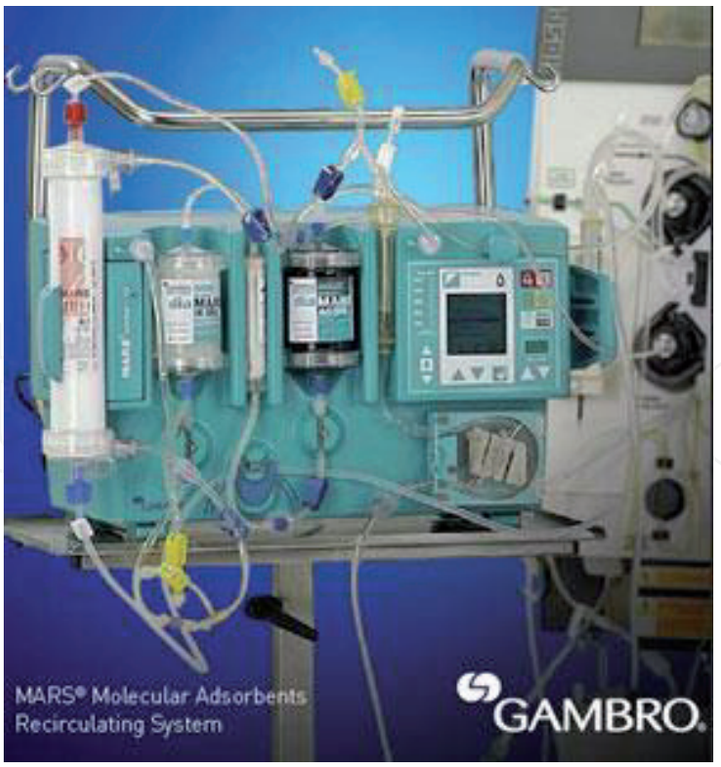

Figure 2.
Cartridges in MARS. Adapted from Tawada Healthcare | Gambro Equipment Supplier.

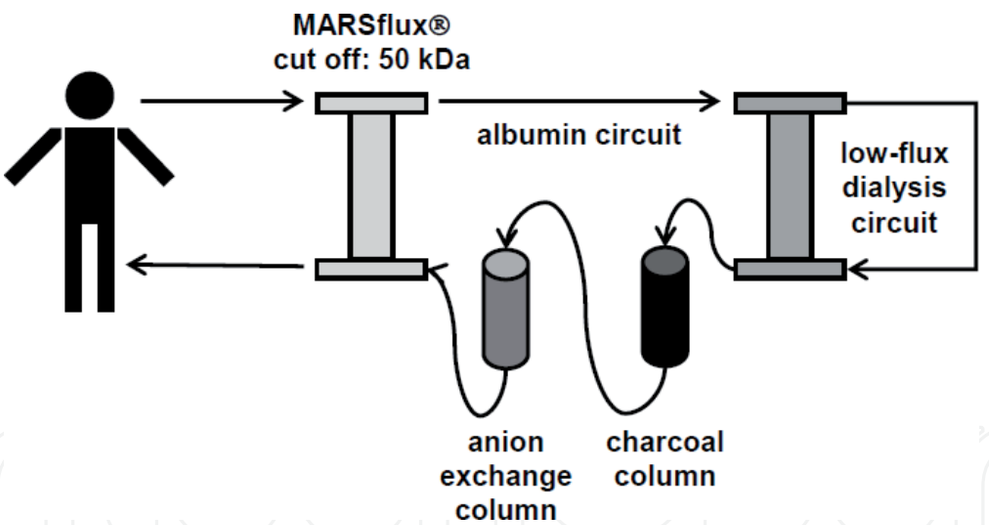

Figure 3.
Schema of the operating principle in MARS. Adapted from Karla et al. Extracorporeal liver support devices for Listed patients. Liver Transplantation 22839–8482016 AASLD.

Interestingly, some authors have been exploring other active substances that can also be eliminated by MARS. In one study, Gay et al. demonstrated that in patients with cholestasis and pruritus, the proteins dialyzed and then absorbed in the anion-exchange resin cartridge of MARS showed elimination of some biologically relevant proteins, such as secreted Ly6/uPAR-related protein-1 (SLURP1) or defensin human neutrophil peptide-1 (HNP-1), which are involved in the inflammatory and defensive processes [17].

When using MARS, particular attention should be given to the monitoring of some critical drugs during treatment, such as fluoroquinolones and meropenem, with dose adjustments done to ensure therapeutic levels.

Anticoagulation during MARS is also essential to consider issue since there is a delicate hemostatic balance that needs to be maintained in patients with liver failure who are at high risk of bleeding. The most used drug in practice is unfractionated heparin, but there are some concerns regarding hemorrhagic risk and heparin-induced thrombocytopenia. Also, some studies have explored the use of continuous extracorporeal systems without anticoagulation and have found a comparable circuit lifespan [18]. The anticoagulant-free approach may also be a reasonable option in patients with a high risk of bleeding. Citrate has been shown to be safe with longer treatment time, preventing filter loss [19]. However, its regular use needs to be validated in an RCT. Unfractionated heparin is the anticoagulant of choice in most clinical trials, but some studies have also used local citrate anticoagulation, with no reported adverse effects [19].

Technical issues have also been raised about the stability of the binding properties of albumin after passing the adsorber columns or about the clinical relevance of some stabilizers (such as octanoate) used in commercially available albumin preparations [20]. However, there are no definitive conclusions, and these issues should be addressed in further studies.

Regarding clinical outcomes, mostly retrospective studies were published in the first years following the debut of MARS. Most of them showed usefulness in the treatment of HE, and some even demonstrated improvement in terms of hemodynamic parameters. The few RCT evaluating survival showed conflicting results [21, 22]. These trials included studied a few patients diagnosed with acute-on-chronic liver failure. In a recent study of 27 patients who received MARS therapy for severe ALF, survival rate was 60% (n = 3/5) for patients with severe liver trauma, 78% (n = 7/9) for patients who used MARS as a bridge to transplantation, and 67% (n = 6/9) when MARS was used as definitive therapy for toxic ingestion or idiopathic liver failure [23].

Lastly, MARS has led us to discover its benefit in drug-induced liver injury (DILI) cases [24]. Statistically speaking, about 50% of cases of ALF are likely due to DILI in the United States [25, 26]. The standard of medical therapy (SMT) is the withdrawal of offending drugs and supportive therapy [27]. A review of the literature indicates several cases of reports of DILI involving several drugs. The most common offending drugs are acetaminophen, nonsteroidal anti-inflammatory drugs, isoniazid, and amoxicillin/clavulanate [28]. However, there are several potential hepatotoxic agents of DILI leading to ALF [29–31].

1.2.2 Fractionated plasma separation and adsorption—FPSA (Prometheus)

Falkenhagen et al. described the first method of FPSA for the use of ALF [32]. The device is shown in **Figure 4**. Prometheus uses endogenous albumin to pass through the circuit using the AlbuFow filter (molecular cut-off of 250 kDa) (**Figure 5**). Albumin is reactivated and returned to circulation using a neutral resin adsorber (Prometh 01) and an anion-exchange column (Prometh 02). Subsequently, the patient's blood then passes through a second circuit, where it is treated by conventional high-flux hemodialysis, eventually returning blood to the patient.

During the first decade of its use in the market, Prometheus showed better efficacy than MARS for both in vitro and in vivo trials in removing ammonia, bilirubin, or bile acids [33]. In 2009, Grodzicki et al. also showed a significant decline in serum ammonia, bilirubin, aspartate aminotransferase, alanine aminotransferase, urea, and creatinine with the use of Prometheus in patients with ALF [34]. Furthermore, Rifai et al. showed a decline in almost all 26 of the amino

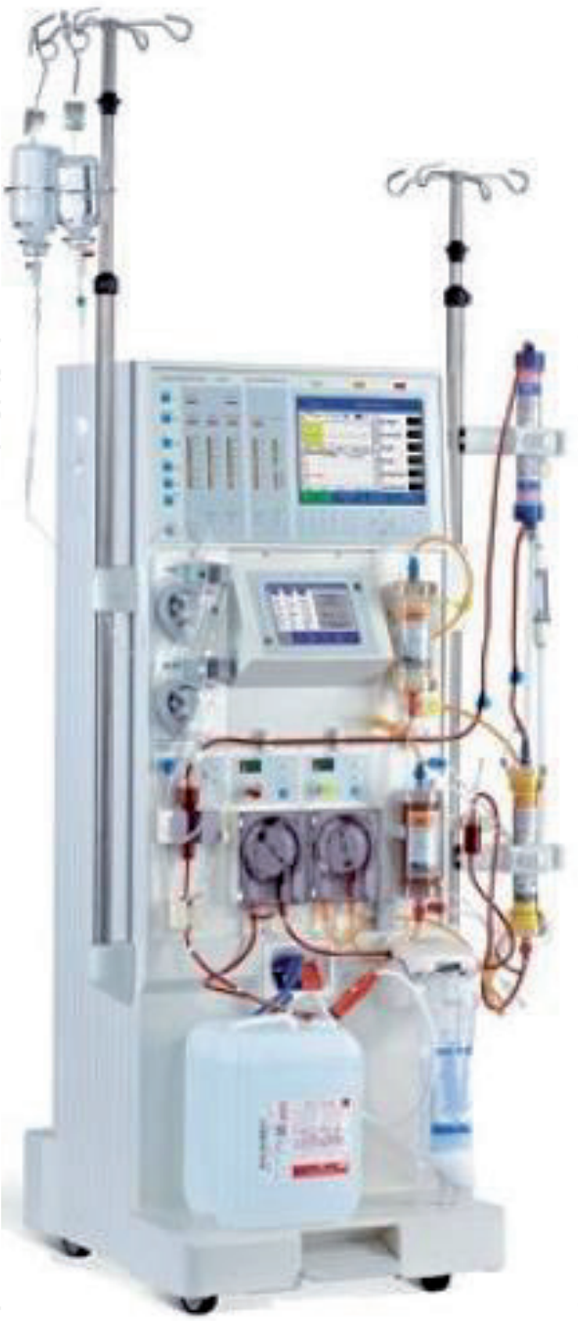

Figure 4.
Fractionated plasma separation and adsorption—FPSA (Prometheus). Adapted from http://dialize.lv. Slokas iela 84-1A, Rīga, LV-1007.

acids measured in nine patients with liver failure with a single treatment session. Prometheus is also hypothesized to improve the complications of HE due to the removal of amino acids such as glutamine, phenylamine, tyrosine, and tryptophan, which all have been noted to be contributing factors to HE, and thus, may help to improve outcomes in patients with liver failure [35]. In an experimental study of ALF by Ryska et al., Prometheus showed a significant decrease in intracranial pressure (ICP) in pigs to that of the control group (24 mmHg versus 29.8 mmHg, respectively, $p < 0.05$) suggesting that its use in the removal of amino acids in that contribute to the development of HE [36].

Rosen et al. also showed a significant reduction in most cytokines and tumor necrosis factor with Prometheus, potentially highlighting its possible role in the treatment of liver failure [37, 38]. Despite showing this drastic decrease, no other

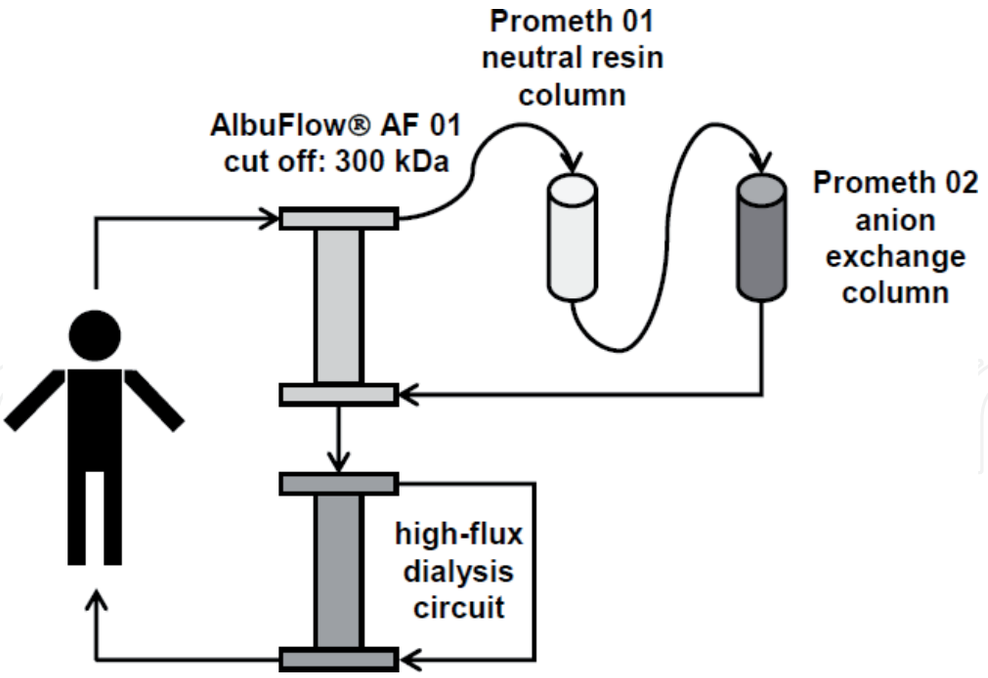

Figure 5.
Schema of Prometheus. Adapted from Karla et al. Extracorporeal Liver support devices for listed patients. Liver Transplantation 22839–8482016 AASLD.

improvement was seen aside from improvement of HE clinically. There was also note of a significant surge in hepatocyte growth factor (HGF) concentration, which stimulates liver regeneration. Similar to MARS, there was no significant impact shown in the cytokine profile, and further research needs to be done in this area of study.

In terms of survival and clinical outcomes, Laleman et al. published an article comparing SMT with MARS and Prometheus in a patient with acute-on-chronic liver failure and it showed MARS to have better outcomes in terms of hemodynamic parameters (mean arterial pressure, stroke volume, systemic resistance) [38]. Dethloff et al. also revealed similar findings in the improvement of mean arterial pressure in patients with decompensated liver cirrhosis with the MARS session as opposed to Prometheus and conventional hemodialysis [39]. Both of the modalities (MARS and Prometheus) decrease cytokines and inflammatory markers; however, there is no exact explanation for these hemodynamic changes.

Kribben et al. in 2012 conducted a multicentric RCT (HELIOS study) comparing Prometheus versus SMT in 145 patients with acute-on-chronic liver failure; the primary endpoints are survival at 28 days and 90 days [19]. The overall survival of the Prometheus group compared to the SMT group was 47% versus 38% but did not show any statistical significance.

In the subgroup analysis of patients with advanced liver disease (MELD >30), there was a significantly higher 90-day survival probability (48% versus 9%, $p < 0.05$) for the Prometheus group compared to SMT. This highlights a possible benefit of Prometheus for treating advance liver disease patients, although the small sample size of the group limits its generalizability to the population.

Over time, other studies derived differing conclusions in regard to its clinical benefit. Sentürk el al. compared the biochemical and clinical parameters for FPSA in patients with ALF and acute-on-chronic liver failure, and showed a significant improvement in the biochemical parameters in HE, although survival rates were not addressed in this study [40]. Similarly, Komardina et al. also showed hemodynamic and biochemical improvements with Prometheus in patients with ALF, but without any difference in survival outcomes [41].

1.2.3 Single-pass albumin dialysis (SPAD)

Single-pass albumin dialysis (SPAD) is a simple technique of blood purification without the sophisticated blood purification line and can be implemented in any intensive care unit applying a standard CRRT. The blood is passed across and dialyzed through a high-flux hollow-fiber hemodiafilter containing albumin-impregnated dialysate, as shown in **Figure 6**. Dialysate is discarded once it passes through the dialyzer, which uses high amounts of exogenous albumin, effectively making it significantly more expensive than MARS, which recycles endogenous albumin [17].

Sauer et al. studied SPAD and MARS, and both were shown to be better than continuous venovenous hemodiafiltration (CVVHD) in removing water-soluble and protein-bound compounds (bilirubin and bile acids) using 4.4% albumin dialysate solution [42]. Kortgen et al. also confirmed these results by comparing the detoxification capacity in patients with liver failure [43]. Both had a significant reduction in serum bilirubin levels, although MARS had a better result in lowering the urea and creatinine level. The limitation of the study was its retrospective and non-randomized nature, and fewer patients were in the SPAD group than there were in the MARS group.

Several studies were conducted to assess the efficacy of dialysate solution concentration for optimal results while carrying out SPAD. Churchwell et al. demonstrated that the highest effectiveness was achieved with 5% albumin dialysate and a larger polysulfone dialyzer (surface area 1.5 m^2). Subsequently, Schmuck et al. and Benyoub et al. demonstrated an optimal detoxification efficacy for albumin-bound substances such as bilirubin and bile acids with a 3–3.2% albumin concentration and a dialysate flow rate of 1000 mL/h using SPAD with a conventional CVVHD and a high-flux polysulfone hemodiafilter [44].

There were only a few case reports published for SPAD immediately after its introduction, and currently, there are no published studies that emphasize on demonstrating the clinical benefits of SPAD versus SMT in ALF. Two uncontrolled retrospective studies in pediatric and adult patients with ALF treated with SPAD as rescue therapy were previously done but neither had conclusive evidence showing their clinical effectiveness, although both noted its ease of use and absence of complications [45].

The most recent RCT done by Sponholz et al. comparing SPAD versus MARS demonstrated a similar decline in the total plasma bilirubin levels, without significant differences between these two LAD modalities [46]. However, the reduction in the total bile acids and γ-glutamyl transferase levels in the patient treated with

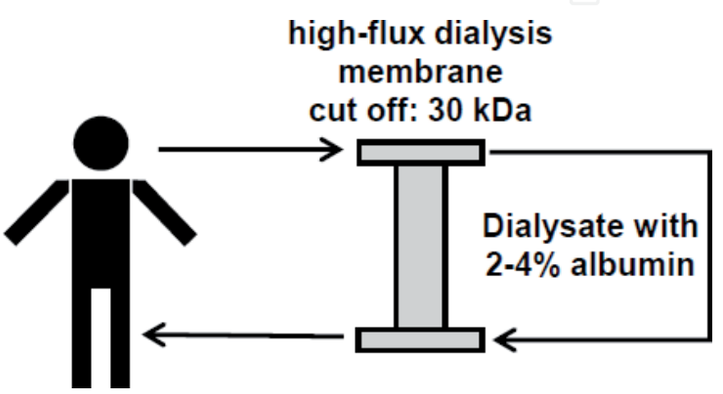

Figure 6.
Schema of SPAD. Adapted from Karla et al. Extracorporeal liver support devices for Listed patients. Liver Transplantation 22839–8482016.

SPAD was non-significant. Furthermore, the creatinine and urea levels were not significantly reduced with SPAD compared to those of MARS. The aforementioned results were differing in other studies, where there was a note of metabolic abnormalities with SPAD, such as a rise in lactate levels or a decline in calcium levels. This could be attributed possibly to the preferential use of citrate anticoagulation with a low dialysis flow rate. In these studies, The MARS and SPAD demonstrated a slight improvement in the HE and hemodynamic status.

Regardless of the ease of administration of SPAD as compared to MARS, the standard albumin dialysate concentration, dialysate flow rate, and standard of care are not yet fully established.

1.3 Other devices

New systems are currently being developed, building on previous knowledge of LADs.

Marangoni et al. described a high-efficiency MARS by incorporating a double adsorption system (double columns containing charcoal and another pair with ion-exchange resin) into the albumin circuit [47]. The detoxification potential of modified MARS was compared with that of the "classical" MARS in four patients with liver failure and demonstrated that "improved" MARS was potentially more efficient in reducing bilirubin and bile acids.

Another system currently being studied conducted by Akcan Arikan et al. presented the usefulness of high-flux CRRT for hyperammonemia, therapeutic plasma exchange for coagulopathy, and MARS for HE. This retrospective observational study showed that 15 pediatric patients with ALF or acute-on-chronic liver failure showed improvement in hepatic encephalopathy with these modalities [48].

More recently, Al-Chalabi et al. and Huber et al. published an animal model of ALF, and patients with liver failure respectively. A modified device called advanced organ support (ADVOS) was first presented in 2013, which included a dialysate circuit containing standard dialysate with a 2–4% albumin concentration, an extracorporeal blood circuit, and a third and last circuit where the albumin dialysate was separated into two parts. Each part would undergo a PH and temperature change before reaching the cation and anion filters, resulting in dialysates that have albumin that is free of toxins [49, 50]. This is accomplished by adding and removing acid or base. The dialysates containing toxin-free albumin then join with each other to reach the expected pH before entering the hemodialyzer again. Huber et al. also showed the same result with ADVOS in reducing bilirubin levels. However, no other studies were further published recently.

Some other modification techniques such as plasma diafiltration, plasma exchange, or therapeutic apheresis using a bilirubin adsorbent column were also published in literature anecdotally [51–53].

1.4 Bioartificial liver support devices

In the last 10 years, significant developments were made with bioartificial liver support devices. These systems are designed to be able to mimic the synthetic and regulatory functions of the liver, in conjunction with the use of LADs to detoxify the patient's plasma. Tumor cell lines, developing expandable progenitor cell populations, or primary human cells can be used, although the most widely used are xenogeneic derivations of primary porcine cells, due to their availability, although there is a risk of infection (i.e., porcine retrovirus infection) and metabolic incompatibility (i.e., graft-versus-host disease, drug-induced thrombocytopenia, complement clotting cascade activation).

1.4.1 Extracorporeal liver assist device (ELAD)

Extracorporeal liver assist device (ELAD) consists of hepatoblastoma C3A cell line, derived from human hepatoblastoma cell line HepG2. Cells are localized in the extra capillary space of a modified dialysis cartridge with a membrane cut-off of 70 kDa to prevent immunoglobulins, blood cells, and C3A tumorigenic cells from crossing [54].

This modality was first developed by Sussman et al. and was assessed in King's College Hospital in London in a pilot-controlled study done by Ellis et al. for patients with ALF who were judged to have >50% survival still and in those who were already indicated for LTx. Twenty-four patients were randomly divided into two groups of ELAD hemoperfusion or control. Overall survival in the ELAD hemoperfusion group was 7 of 9 (78%), and survival for the controls was unexpectedly high, 6 of 8 (75%). Due to the small sample size, the study failed to prove an improvement in the survival rate of patients with ALF [55].

Working off of the initial ELAD, Millis et al. studied a modified version of ELAD to determine the safety profile of the device for patients with fulminant hepatic failure [56]. All patients successfully had an LTx, with four out of the five patients surviving the 30-day survival endpoint of the study, with no noted biomechanical problems or hemodynamic instability. The authors concluded that ELAD is safe and can be conducted on a larger scale in multi-center RCTs.

1.4.2 Bioartificial liver—HepatAssist

Bioartificial liver (BAL) works on the concept of combining hepatocyte bioreactor with a column filled with cultured hepatocytes to mimic liver function. Arbios first described BAL devices, which the Food and Drug Administration approved for Phase I, II, and III clinical trials. In HepatAssist, the patient's blood is initially separated into plasma and cellular components. The plasma is then passed through a high-flow plasma circulation loop and then successively through a charcoal filter, oxygenator, heater, and a hollow fiber bioreactor containing 7 billion cryopreserved hepatocytes. The resulting processed plasma then combines again with the cellular components and sent back to the patient's blood [3].

In the study of Watanabe et al., 31 patients were enrolled in a Phase I study, with the goal of developing a BAL for patients with severe liver failure until they can be transplanted or recover spontaneously [57]. Sixteen out of 18 (89%) patients in group 1 were successfully bridged to LTx. The same goes for group 2 patients (n = 3); all were bridged successfully to transplantation, while group 3 (n = 10) had two who were supported to recovery and LTx. The remaining eight patients in group 3 expired since they were not candidates for LTx.

Other Phase II and III clinical trials from multiple centers across US and European centers involving 171 patients (86 controls and 85 treated) were conducted to study the efficacy of this device in patients with ALF. Inclusion criteria were patients with Stage III or IV HE or with primary non-function of the transplanted liver. The groups were randomized, receiving standard of care and daily treatment with HepatAssist for 7 hours. Results for this trial were inconclusive and failed to show an improvement in 30-day survival rates, although a good safety profile was noted.

Subgroup analysis indicated that the HepatAssist session might provide an improvement in survival rate in patients, especially with drug and chemical toxicity-induced liver failure [58]. Recently, according to Arbios Systems, Inc., there is a study underway to assess a version of HepatAssist with 15–20 billion porcine hepatocytes to be studied in Phase III clinical trials [3].

1.4.3 Modular extracorporeal liver support (MELS)

Modular extracorporeal liver support (MELS) was developed in Germany and is based on tailoring the extracorporeal therapy units to the clinical need of the patient. In a Phase I study using porcine hepatocytes-based BALs, eight patients with ALF showed that it might be beneficial as a bridge to a liver transplant. The limitations are its high cost and complicated design, which may become an obstacle for its wide availability [3].

1.4.4 Academic Medical Center (Amsterdam)-BAL

In contrary to other BAL support devices, this modality is incorporated with capillaries for oxygenation and viability [54]. Preliminary studies are promising; however, more extensive trials are needed to validate its efficacy.

When comparing MELS to AMC-BAL, both have shown comparable efficiency. Although in one study, it was demonstrated that ammonia and lidocaine removal was significantly higher in AMC-BAL as compared to MELS. However, LDH was observed to be considerably lower in MELS.

Several other liver support devices have been developed across the world such as the Hybrid-BAL (Nanjing, China), TECA-Hybrid Artificial Liver Support System (Beijing, China), the Bioartificial Hepatic Support (Udine, Italy), and the Radial Flow Bioreactor (Ferrara, Italy), although further research is required to assess their efficacy and safety [59].

2. Conclusion

ALF, despite being treated medically, is linked with high mortality. Due to longer wait time for liver donors in patients who require LTx, many patients with ALF will, unfortunately, die while waiting for a transplant. Therefore, a liver support system is necessary as a "bridge" to final treatment or until the liver regenerates upon removal of the inciting cause. Over the last 20 years, many artificial liver support systems with the potential to emerge as an ideal device with advances have been introduced. At present, whether BALs can reduce mortality in the ALF population remains controversial.

BALs incorporating human primary hepatocytes are the most suitable cells but are limited by low availability due to a shortage of donor organs. The development of an implantable liver system where hepatocytes can be cultured on substrates to mimic the lobular structure of the liver is promising. However, mimicking the vascular and biliary connections of the liver and recreating all of the necessary metabolic and biochemical functions of the liver will be challenging. As technology is continually evolving, only time will tell the future of these innovative liver assist devices and their possible impact on human culture and health and well-being of affected individuals.

Conflict of interest

None.

Abbreviations

ALD	artificial liver assist device
BLD	bioartificial liver assist device

MARS	molecular adsorbent recirculating system
ALF	acute liver failure
RCT	randomized clinical trial
SIRS	systemic inflammatory response syndrome
FPSA	fractionated plasma separation and adsorption
MELD	model for end-stage liver disease
CVVHD	continuous venovenous hemodiafiltration
SPAD	single-pass albumin dialysis
ELAD	extracorporeal liver assist device
MELS	modular extracorporeal liver support

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