

## REVIEW ARTICLE

# Extracorporeal Liver Support in Liver Failure: A Comprehensive Review of MARS, SPAD, Prometheus, ADVOS, and Bioartificial Systems

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### ABSTRACT

**Background** : Acute and chronic liver failure are life-threatening conditions often requiring liver transplantation as definitive therapy. To delay or substitute the need for transplantation, various extracorporeal liver support systems have been developed. This article aims to review current artificial and bioartificial liver support systems including the Molecular Adsorbent Recirculating System (MARS), Single Pass Albumin Dialysis (SPAD), Prometheus, ADVanced Organ Support (ADVOS), and Bioartificial Liver (BAL) devices.

**Discussion** : MARS and SPAD utilize albumin-based dialysis to remove protein-bound and water-soluble toxins. Prometheus applies a fractionated plasma separation and adsorption approach, while ADVOS enables individualized acid-base correction. Bioartificial liver systems integrate hepatocyte bioreactors with plasma dialysis to provide more physiological metabolic support. While these systems show promise in improving clinical outcomes, long-term survival benefit remains under investigation.

**Conclusion** : Extracorporeal liver support systems offer essential bridging and supportive therapies for patients with liver failure. Selection should be tailored to patient condition, therapeutic goals, and technology availability.

**Keywords**: ADVOS; Albumin Dialysis; Bioartificial Liver; Liver failure; MARS; Prometheus; SPAD.

## INTRODUCTION

Acute and chronic liver failure remain life-threatening conditions associated with high morbidity and mortality, particularly in the absence of timely liver transplantation. Despite advances in supportive care, liver transplantation remains the only definitive treatment for end-stage liver failure. However, due to the scarcity of donor organs, high costs, and medical contraindications in critically ill patients, many are either ineligible for or unable to undergo transplantation in a timely manner. This unmet need has prompted the development of extracorporeal liver support systems as bridging therapies to transplantation or recovery.

In recent decades, a variety of artificial and bioartificial liver support systems have been introduced to mimic the detoxification, regulation, and synthetic functions of the native liver. Among these, the Molecular Adsorbent Recirculating System (MARS), Single-Pass Albumin Dialysis (SPAD), and Prometheus represent non-biological systems primarily focused on toxin removal, particularly albumin-bound toxins<sup>1-3</sup>. More recently, the ADVanced Organ Support (ADVOS) system has been developed to provide integrated

support for multiple organ systems, including correction of acid-base imbalances<sup>4</sup>. In contrast, bioartificial liver support systems incorporate functional hepatocytes to provide both detoxification and limited synthetic functions, aiming to more closely replicate the metabolic profile of the liver<sup>5</sup>.

Despite significant technical advancements, the clinical utility and survival benefit of these modalities remain areas of ongoing investigation. Understanding the mechanisms, advantages, and limitations of each system is essential for selecting appropriate liver support strategies in critically ill patients. This manuscript provides a comprehensive review of the most widely used extracorporeal liver support systems, including MARS, SPAD, Prometheus, ADVOS, and bioartificial liver devices, with an emphasis on their mechanisms of action, clinical applications, and potential role as bridging therapies in liver failure.

Given the complexity of liver failure, initiation and tailoring of extracorporeal liver support require a structured multidisciplinary process. The anesthesiologist and intensivist assess perioperative and ICU physiology

including ventilation, vasopressor needs, and anticoagulation strategy. The hepatologist determines the liver disease trajectory, transplant candidacy, and encephalopathy management. The nephrologist evaluates renal replacement needs, membrane choice, and solute clearance targets. Decisions are individualized by balancing expected toxin removal, acid–base control, and hemodynamic effects with bleeding risk, circuit feasibility, staffing, and local resources. The team should agree on indications, monitoring checkpoints, and stopping rules aligned with goals of care such as bridge to transplant or bridge to recovery.

## DISCUSSION

Extensive research efforts have been directed toward delaying or preventing the need for liver transplantation in patients with acute liver failure. Among the most investigated therapeutic modalities are artificial liver support systems, auxiliary liver transplantation, liver dialysis technologies, and xenotransplantation. Several liver assist devices (LADs) were developed in the 1990s based on the pathophysiology of albumin dialysis. The most widely recognized systems include the Molecular Adsorbent

Recirculating System (MARS), Single Pass Albumin Dialysis (SPAD), and the Fractionated Plasma Separation and Adsorption (FPSA) system, known as Prometheus. These modalities are specifically designed to remove albumin-bound toxins that accumulate during hepatic failure. LADs also facilitate the removal of water-soluble substances such as ammonia, urea, and small proteins including various cytokines through standard dialysis mechanisms<sup>1</sup>.

The elimination of cytokines and other known contributors to hepatic encephalopathy (HE), including amino acids such as tryptophan and glutamine, has been demonstrated to mitigate the severity of HE and lower the risk of complications associated with liver failure. In addition, these systems enhance the clearance of both conjugated and unconjugated bilirubin, protoporphyrins, bile acids, glycoside derivatives, phenols, and short- to medium-chain fatty acids like octanoate, as well as various heterocyclic organic compounds. Notably, one study reported that the removal of plasma nitric oxide (NO), together with several pro- and anti-inflammatory cytokines, was correlated with clinical improvements in

HE, renal and respiratory functions, stabilization of hemodynamic parameters, and a reduction in the progression of multiorgan failure.

Liver assist devices designed for patients with acute liver failure are broadly categorized into two main groups: non-cell-based systems (such as plasmapheresis, plasma exchange, albumin dialysis, or charcoal-based hemadsorption) and cell-based systems, commonly referred to as bioartificial liver support systems, which incorporate functional hepatic tissue.

Liver support systems can be classified into biological and mechanical modalities. Among artificial (mechanical) systems, MARS and SPAD can remove toxins effectively. Despite being artificial systems, MARS and SPAD only provide detoxification support without offering synthetic liver functions and have not been shown to improve survival outcomes in clinical studies.

### **Molecular Adsorbent Recirculating System (MARS)**

First introduced in 1990, the Molecular Adsorbent Recirculating System (MARS) has since become the most extensively documented and clinically implemented artificial liver

support modality to date<sup>1</sup>. Its clinical utilization began in 1998 and is grounded in two key physiological principles: the affinity of albumin for protein-bound toxins and the diffusion of solutes across a concentration gradient. The MARS configuration incorporates several integrated components, including an albumin-specific hemodialyzer, a conventional hemodialyzer, an activated charcoal adsorbent, and an anion exchange resin. This system consists of dual-phase approach: initial detoxification using an albumin-containing dialysate to remove protein-bound toxins, followed by conventional hemodialysis to remove water-soluble toxins, this process facilitated by the MARS Flux Dialyser. This dialysis consists of a blood circuit, an albumin circuit (containing 600 mL of 20% human albumin, a charcoal column, and an anion exchange column with cholestyramine), and a traditional “renal” dialysate circuit as shown<sup>1</sup>.

The mechanism of action of the MARS system involves two main operational systems<sup>1</sup>:

1. In the initial phase of MARS therapy, blood is directed through a high-flux dialysis membrane that interfaces with an albumin-containing solution. This

membrane facilitates the transfer of both water-soluble and hydrophobic protein-bound toxins into the dialysate via diffusion, a process predominantly governed by the concentration gradient and the molar ratio between toxins and albumin. The albumin dialysate is recirculated continuously, maintaining its capacity to bind further toxins until the adsorbent columns reach saturation. As such, repeated albumin replacement is unnecessary during the session. Beyond its detoxification capabilities, MARS has also demonstrated the potential to modulate systemic inflammation through cytokine clearance, which is particularly relevant in the context of liver failure. Inflammatory cytokines are central to the progression of hepatic encephalopathy, systemic inflammatory response syndrome (SIRS), vasodilation, and multiple organ dysfunction. These mediators contribute to hepatocellular injury, cholestasis, and programmed cell death. Empirical evidence has shown that MARS therapy effectively reduces circulating levels of several pro-inflammatory cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-6, and IL-1, along with the anti-inflammatory cytokine IL-10.

Nevertheless, not all investigations have observed significant changes in plasma cytokine levels, potentially due to continued endogenous cytokine production that may offset extracorporeal removal.

In the second step, the ultrafiltrate passes through the hemodialysis circuit, where all water-soluble toxins are removed, and the blood is subsequently returned to the patient. The dialysate flows through a third compartment that contains a bicarbonate-buffered solution. Following this process, the cleansed blood is reinfused into the patient's circulation.

When using MARS, special attention must be given to the monitoring of certain critical medications, such as fluoroquinolones and meropenem, by adjusting their dosages to maintain therapeutic levels. Anticoagulant use should also be carefully considered, as patients are at increased risk of bleeding.

MARS therapy has demonstrated effectiveness in removing aromatic amino acids and substantial elimination of albumin-bound toxins such as fatty acids, bile acids, tryptophan, and bilirubin. The removal rates of bilirubin and bile acids during a single session

range from approximately 28% to 55%. Bilirubin clearance typically shows a decline after 6 hours of therapy<sup>1,2</sup>. Physiologically important proteins, including albumin, alpha-1 glycoprotein, alpha-1 antitrypsin, alpha-2 macroglobulin, transferrin, and thyroxine-binding globulin, as well as hormones such as thyroxine and thyroid-stimulating hormone, are not significantly removed<sup>2</sup>.

Albumin can bind to fatty acids, hormones, enzymes, dyes, mineral elements, and various drugs, thus playing a critical role in toxin clearance. In patients with liver dysfunction, the removal of albumin-bound toxins creates a more favorable environment for hepatocyte recovery and regeneration, while also providing time for the resolution of precipitating factors such as infection or gastrointestinal bleeding<sup>2</sup>.

Ammonia, a water-soluble compound, is significantly eliminated during MARS therapy, which enhances its efficacy in addressing complications associated with hepatic failure. In addition to its primary function in hepatic detoxification, MARS has demonstrated clinical utility in the management of uremia. Furthermore, the system has exhibited the capacity to

remove nitric oxide, a vasoactive mediator that plays a critical role in circulatory dysregulation during liver failure. Collectively, these mechanisms contribute to improved hemodynamic stability, as evidenced by an increase in MAP and a decreased reliance on vasopressor agents. Additionally, neurological benefits have been reported, including improvements in the grades of hepatic encephalopathy and a reduction in intracranial pressure levels.

Therapy duration ranges from 6 to 24 hours depending on the patient's hemodynamic status. Literature recommendations suggest intermittent therapy for 6–8 hours in hemodynamically stable patients and continuous therapy for unstable patients. The albumin pump rate is typically maintained at 150 mL/min unless excessive circuit pressure necessitates a reduction. Continuous venovenous hemodialysis (CVVHD) is commonly used, with dialysate flow rates varying between 8.3 and 25 mL/min depending on the need for uremia control. Lactate-free dialysate solutions have been employed. Vascular access is achieved using a double-lumen catheter<sup>2</sup>.

The MARS machine operates with two pumps, one derived from a

hemodialysis or CVVH machine. A closed-loop albumin circuit connects the blood and dialysate circuits and is controlled by a pump monitored through the MARS system. The MARS flux membrane is impermeable to proteins larger than 50 kDa (e.g., growth factors), which are unable to diffuse across the membrane<sup>6</sup>.

Blood pump flow rates range from 100 to 250 mL/min depending on vascular access quality and circuit pressure. Anticoagulation within the extracorporeal circuit is achieved using a combination of epoprostenol (5 ng/kg/min) and heparin, with heparin dosing adjusted to maintain an activated partial thromboplastin time (APTT) of 50–60 seconds<sup>2</sup>.

The primary indications for MARS therapy include decompensated chronic liver disease (either for recompensation or as a bridge to liver transplantation), acute liver failure, post-transplant liver failure, and secondary liver failure associated with multi-organ failure or dysfunction. Secondary indications include refractory pruritus in cholestatic liver disease and hepatic failure following liver surgery<sup>2</sup>.

Several lines of evidence support the clinical efficacy of MARS. Notably,

the MARS system exhibits a unique capacity to selectively eliminate both water-soluble and albumin-bound toxins, including nitric oxide, which plays a significant role in the systemic manifestations associated with liver failure. Clinical findings indicate that the utilization of MARS is correlated with enhancements in neurological status, hemodynamic parameters, renal function, and the overall performance of multiple end organs. Furthermore, the system's antioxidant properties have been shown to contribute to the reduction of oxidative stress, a recognized factor that exacerbates the progression of hepatic injury. It has demonstrated therapeutic versatility in managing intoxications involving protein-bound pharmacologic agents, such as phenytoin, theophylline, and lamotrigine.

**Table 1.** Dialysate elements in MARS depend on affinity

| Water solubel | Albumin Bound                        |
|---------------|--------------------------------------|
| Ammonia       | Bilirubin (indirect, principally)    |
| Urea          | Bile salt                            |
| Creatinin     | Tryptofan                            |
|               | Fatty acid (medium-/short-chain)     |
|               | TNF- $\alpha$ , IL-6                 |
|               | Copper                               |
|               | Benzodiazepin (principally diazepam) |



## Single Pass Albumin Dialysis (SPAD)

To bridge the waiting period for liver transplantation or in cases of acute liver failure, liver function replacement therapies such as Single Pass Albumin Dialysis (SPAD) have been developed as alternative treatment options. SPAD is a dialysis-based liver support system designed to eliminate toxic substances that cannot be cleared by the body due to liver failure. It utilizes albumin as a toxin carrier, enabling the detoxification of protein-bound substances such as bilirubin, bile acids, and other compounds that are difficult to eliminate through conventional dialysis.

SPAD consists of a standard continuous renal replacement therapy (CRRT) system using a high-flux membrane that is impermeable to albumin. Plasma flows countercurrent to a dialysate solution containing 5% albumin. Low-molecular-weight toxins bound to albumin diffuse along their concentration gradient and bind to the albumin in the dialysate before being removed. The basic mechanism of SPAD is as follows<sup>3</sup>:

- The patient's blood is circulated through a dialysis system.
- During this process, the albumin-containing dialysate binds to toxins

such as bilirubin and bile acids that have accumulated due to liver dysfunction.

- The toxin-bound albumin is then discarded with the dialysate in a single-pass process and eliminated from the body.

Albumin serves as the primary carrier due to its strong binding affinity for hydrophobic molecules and other high-affinity substances that cannot be effectively removed by conventional dialysis methods. In SPAD, albumin is continuously infused in a single-pass system without recirculation, distinguishing it from other techniques such as the Molecular Adsorbent Recirculating System (MARS). SPAD offers several advantages over other dialysis-based methods<sup>3</sup>:

- High efficiency in toxin removal: The use of albumin enables SPAD to eliminate protein-bound toxins that cannot be cleared through standard dialysis.
- Lower cost: Unlike MARS, which requires a more complex and expensive setup, SPAD can be performed using modified conventional dialysis machines, making it more cost-effective.



- **Simplicity:** SPAD is relatively simple from a technical standpoint and requires only minimal modifications to standard dialysis equipment.

Multiple clinical studies have demonstrated that SPAD is effective in reducing serum concentrations of bilirubin, bile acids, and other toxic substances in patients with liver failure. Several investigations have also reported improvements in neurological function among patients with hepatic encephalopathy following SPAD therapy. However, despite its efficacy as a temporary support modality, SPAD does not address the underlying cause of liver disease, and thus, liver transplantation remains the definitive treatment option<sup>3</sup>.

SPAD is frequently compared with other liver support therapies such as MARS and Prometheus:

- **MARS:** MARS utilizes recirculated albumin within a closed system, whereas SPAD uses single-pass albumin without recirculation. MARS is more complex and costly but offers greater control over the dialysis process.

- **Prometheus:** Prometheus employs a technology that combines adsorption with plasma dialysis, in contrast to SPAD's simpler approach using albumin alone. SPAD is more accessible and can be more easily implemented in a wider range of clinical settings.

SPAD represents an important innovation in liver replacement therapy, particularly for patients with acute or chronic liver failure who require temporary support prior to transplantation or spontaneous hepatic recovery. Through a mechanism that uses albumin's ability to bind and remove toxins, SPAD has proven to be effective and more cost-efficient compared to other methods such as MARS. Nonetheless, SPAD remains a temporary solution, and liver transplantation is still required for long-term recovery in patients with severe liver failure.

### **Prometheus**

Prometheus represents an artificial liver support system that operates on the principle of albumin dialysis, employing a purification technique termed Fractionated Plasma Separation and Adsorption (FPSA), originally introduced by Falkenhagen.

This system is uniquely designed to simultaneously remove both albumin-bound and water-soluble toxins through a mechanism distinct from that utilized by MARS. Unlike MARS, which applies an albumin-impermeable membrane to facilitate toxin removal via diffusion, Prometheus incorporates an albumin-permeable polysulfone membrane (AlbuFlow).

This allows the separation of the albumin fraction containing bound toxins from the patient's blood into a secondary circuit. Within this circuit, specialized adsorber columns (Prometh 1 and Prometh 2) are employed to directly purify the toxin-laden albumin. In parallel, conventional high-flux dialysis is conducted in the primary circuit to eliminate water-soluble compounds.

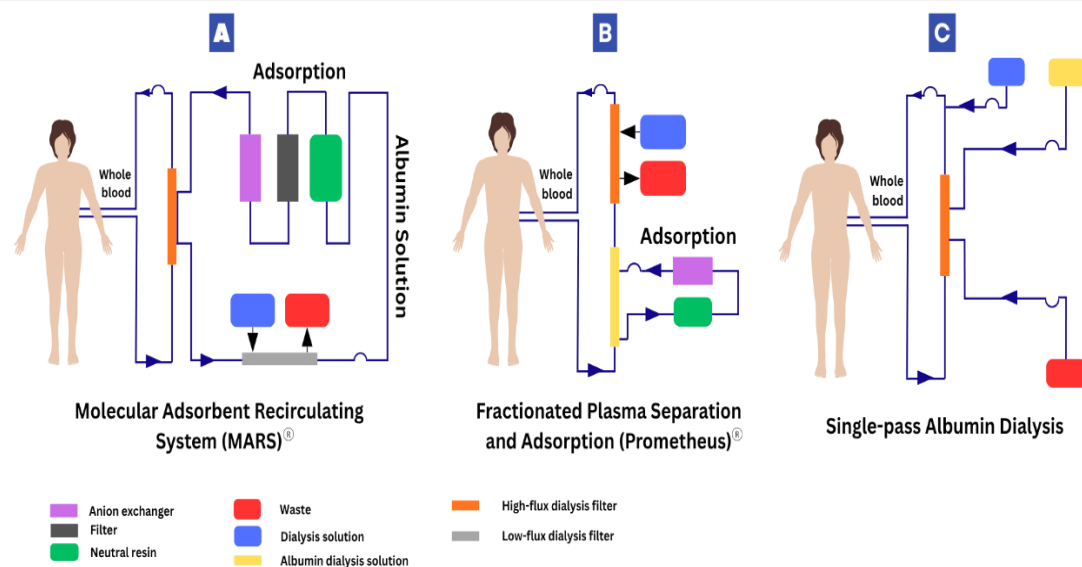
These dual processes are integrated through a modified hemodialysis platform comprising two distinct control systems, enabling either standard hemodialysis or its combination with albumin-based detoxification. Clinically, Prometheus therapy is typically administered over an average duration of  $5.1 \pm 1.1$  hours, with a mean blood flow rate of  $193 \pm 10$  mL/min. The

system processes a total blood volume of approximately  $58 \pm 14$  liters per session<sup>7</sup>.

The removal rates of total and conjugated bilirubin, bile acids, creatinine, and urea using Prometheus range from 41% to 68%. However, serum ammonia removal is relatively low, approximately 17%, which may be attributed to high rates of ammonia production or redistribution<sup>7</sup>.

One notable advantage of Prometheus over the MARS system is its ability to remove unconjugated bilirubin. Except for bile acids, all substances demonstrate higher clearance and reduction ratios with Prometheus compared to MARS.

Systemic hemodynamics have also been evaluated, showing improvements in mean arterial pressure (MAP) and peripheral resistance in patients treated with MARS. These effects may be related to the elimination of vasoactive agents such as renin and nitric oxide (NO), which occurs with MARS but not with Prometheus, and may also be influenced by the unintended loss of endogenous albumin during Prometheus therapy<sup>7</sup>.



**Figure 1.** Schematic Differences Between MARS, SPAD, and Prometheus

Prometheus is a liver support therapy with several clinical indications. The primary indications include acute liver failure, acute-on-chronic liver failure, acute alcoholic hepatitis, hepatorenal syndrome, hepatic encephalopathy, and its use as a bridging therapy to liver transplantation. Additionally, Prometheus therapy may be employed to manage refractory pruritus due to cholestasis and intoxication with protein-bound drugs<sup>7</sup>.

However, there are several contraindications that must be considered before initiating this therapy. Prometheus should not be used in patients with uncontrolled bleeding, severe hemodynamic instability, uncontrolled septicemia, disseminated intravascular

coagulation (DIC), or severe thrombocytopenia. Therefore, a thorough clinical assessment is essential to determine the suitability of Prometheus therapy for each patient<sup>7</sup>.

### ADVOS (Advanced Organ Support)

ADVanced Organ Support (ADVOS) is the most recent albumin dialysis procedure, introduced in 2013, capable of eliminating both water-soluble and albumin-bound substances. It also allows for the correction of acid-base imbalances through the individualized adjustment of dialysate composition. The dialysate formulation, including its acid-base parameters (including pH), is automatically tailored to meet the specific needs of each patient to maintain acid-base homeostasis.

Patients eligible for ADVOS therapy include those with acute kidney injury (AKI), hypoxic liver injury, cardiogenic shock, and septic shock. ADVOS is primarily initiated in patients with stage 3 AKI and acute-on-chronic liver failure.

The ADVOS system consists of three circuits: (1) the extracorporeal blood circuit, (2) the dialysate circuit, and (3) the ADVOS multi-circuit. The blood circuit includes two high-flux polyethersulfone filters (Surelyzer PRS 190 DH) with an effective surface area of 1.9 m<sup>2</sup>, and a blood flow rate ranging from 100 to 400 mL/min.

The dialysate and ADVOS circuits work in tandem to remove both protein-bound and water-soluble toxins from the patient's blood. The dialysate contains 200 mL of 20% albumin and is recirculated at a flow rate of 800 mL/min through the second circuit. Albumin dialysate binds protein-bound toxins, while unbound toxins diffuse across the semipermeable dialysis membrane<sup>4</sup>.

The albumin's binding capacity is then restored through the parallel addition of acid and base concentrates (at flow rates of 160–320 mL/min) in the ADVOS circuit, producing a dialysate with the

following concentrations (mmol/L): Na 133–145, Cl 100–106, K 2.8, Ca<sup>2+</sup> 1.15–1.22, Mg<sup>2+</sup> 0.5, HPO<sub>4</sub> 0.5, HCO<sub>3</sub> 25–26. In addition, 40% glucose (70 mL/h) is infused into the dialysate via an auxiliary port. Toxins are further released and filtered through two high-flux polynephron filters (effective surface area: 1.3 m<sup>2</sup> each), with each filter responsible for either the acidic or basic pathway. Due to differences in pH, cationic toxins (e.g., copper) and anionic toxins (e.g., bilirubin) can be dissociated from albumin and subsequently removed<sup>4</sup>.

Compared to previous prototypes, the current generation of ADVOS includes enhanced automatic control mechanisms that allow for dialysate acid-base composition adjustment. The dialysate pH can be set between 7.2 and 9, and the system automatically adjusts dialysate composition based on the volume of each concentrate delivered. In this setup, albumin acts as the primary buffer instead of bicarbonate. As a weak acid, albumin can bind Na<sup>+</sup> or Cl<sup>−</sup>, alter the strong ion difference (SID), and modify dialysate pH. A higher SID and pH in the dialysate promote the reduction of H<sup>+</sup> ions in the blood. In this way, ADVOS may serve as a form of "renal

compensation" for acidosis by shifting the CO<sub>2</sub> equilibrium toward bicarbonate formation<sup>4</sup>.

The median duration of ADVOS therapy is 17.5 hours (range: 11–23 hours) per session. The average blood flow is 100 mL/min, with concentrate flow averaging 160 mL/min, and median ultrafiltration rate at 100 mL/h. Overall, significant improvements in blood pH, bicarbonate (HCO<sub>3</sub><sup>-</sup>), and partial pressure of carbon dioxide (PCO<sub>2</sub>) can be achieved during therapy. Reductions in PCO<sub>2</sub> and increases in systemic pH are influenced by two primary variables: the acid-base composition of the dialysate (set according to the prescribed pH) and the device's blood flow rate. While blood flow correlates with PCO<sub>2</sub> reduction, dialysate pH is significantly associated with changes in systemic pH, HCO<sub>3</sub><sup>-</sup>, and PCO<sub>2</sub><sup>4</sup>.

In patients with acute respiratory distress syndrome (ARDS), ADVOS therapy leads to improvements in pH and PCO<sub>2</sub>, accompanied by reductions in driving pressure and peak inspiratory pressure. Driving pressure improved in 75% of sessions and was associated with baseline values prior to therapy. However, there was a tendency for

decreased tidal volume and minute ventilation following ADVOS, even with reduced ventilatory support<sup>4</sup>.

Hemodynamic parameters improved during ADVOS therapy. Norepinephrine requirements were significantly reduced and MAP increased post-treatment. Therapy can be maintained for up to 24 hours using 200 mL of 20% albumin and low blood flow rates (e.g., 100 mL/min), facilitating effective detoxification across compartments and adequate ultrafiltration. pH modulation in the ADVOS multi-circuit contributes to the release of protein-bound toxins from albumin, enabling both convective and diffusive clearance of solutes<sup>4</sup>.

Changes in acid-base composition, achieved by setting a high dialysate pH, support the normalization of systemic blood pH at low blood flow rates (100–200 mL/min) within 6 hours, even in patients unresponsive to conventional renal replacement therapy. A dialysate pH-driven reduction in PCO<sub>2</sub> up to 40 mmHg between the inlet and outlet of the dialyzer has been observed. In the bloodstream, CO<sub>2</sub> is converted into HCO<sub>3</sub><sup>-</sup> and H<sup>+</sup>. A high dialysate pH establishes a favorable gradient for H<sup>+</sup>

transfer from blood to dialysate. The dialysate contains 20–24 mmol/L bicarbonate, enabling additional gradients for  $\text{HCO}_3^-$  exchange. Consequently,  $\text{PCO}_2$  can be reduced by removing  $\text{HCO}_3^-$  and compensating for metabolic acidosis. This mechanism is further explained by Stewart's quantitative approach, based on changes in the strong ion difference (SID). This process is only feasible due to the enhanced buffering capacity of the dialysate provided by albumin, which, through imidazole side chains, enables the dialysate to modulate acid-base balance according to the targeted pH. Although this reduction in  $\text{PCO}_2$ , together with metabolic acid-base regulation, appears to correct acidosis *in vitro*, these findings remain associative and lack definitive evidence of causality<sup>4</sup>.

### **Modular Ekstracorporeal Liver Support: Bioartificial Liver Support (BAL)**

Isolated hepatocytes have been applied in various configurations, including suspended, substrate-attached, and encapsulated within semipermeable membranes. These hepatocytes, when employed for liver support purposes, are generally categorized into two main

groups: implantable systems and extracorporeal configurations.

In 1987, the first clinical application of a BAL support system was reported. The principle of this BAL system involved hemodialysis with a flow rate of 145 mL/min against a suspension of  $10 \times 10^6$  functional, cryopreserved rabbit hepatocytes. The patient's blood was separated from the rabbit hepatocytes by a cellulose membrane permeable to small and medium-sized molecules. The bioreactor was placed between the radial artery and basilic vein. The BAL device contained  $40 \times 10^6$  porcine hepatocytes within 20 mL of polychlorovinyl capsules. These capsules included a nylon filter at the outlet filled with activated charcoal and organic quartz glass beads. The capsules were inserted into an arteriovenous shunt in the forearm. Each capsule was replaced every six hours, with a blood flow rate through the bioreactor of 90 mL/min<sup>5</sup>.

The cell module is a bioreactor filled with primary human hepatocytes obtained from donor livers deemed unsuitable for transplantation due to steatosis, cirrhosis, or traumatic injury. The detox module facilitates albumin dialysis to remove albumin-bound toxins,



reducing the biochemical burden on hepatocytes and replacing bile excretion function within the bioreactor. The liver support system consists of a blood circuit with a plasma separator unit (Multifiltrate), a high-flux dialysis filter, and a second circuit containing the bioreactor for plasma perfusion. The system can be integrated with standard renal replacement therapy<sup>5</sup>.

Blood is pumped through a hollow fiber plasma filter (Plasmaselect 0.4, Braund) at a flow rate of 150–250 mL/min. The cell module, connected to the plasma circuit, allows countercurrent flow at 150–200 mL/min. The total extracorporeal volume includes approximately 110 mL in the blood circuit and 900 mL of plasma in the bioreactor and associated circuit<sup>5</sup>.

In the continued development of bioartificial liver systems, the MELS CellModule represents one of the most advanced configurations. This includes contributions by Chamuleau and the HepArt company, as well as the BR0600 multicompartiment bioreactor developed by J.C. Gerlach and supplied by Hybrid Organ GmbH. Independent interconnected hollow fiber bundles serve three primary functions: inflow of

medium, cell oxygenation and carbon dioxide removal, and outflow medium. A polyethersulfone membrane with a molecular weight cut-off of >400,000 Da and a total surface area of 2.11 m<sup>2</sup> is used for mass exchange, while a multi-laminated hydrophobic hollow fiber membrane system with a total surface area of 2.22 m<sup>2</sup> facilitates gas supply.

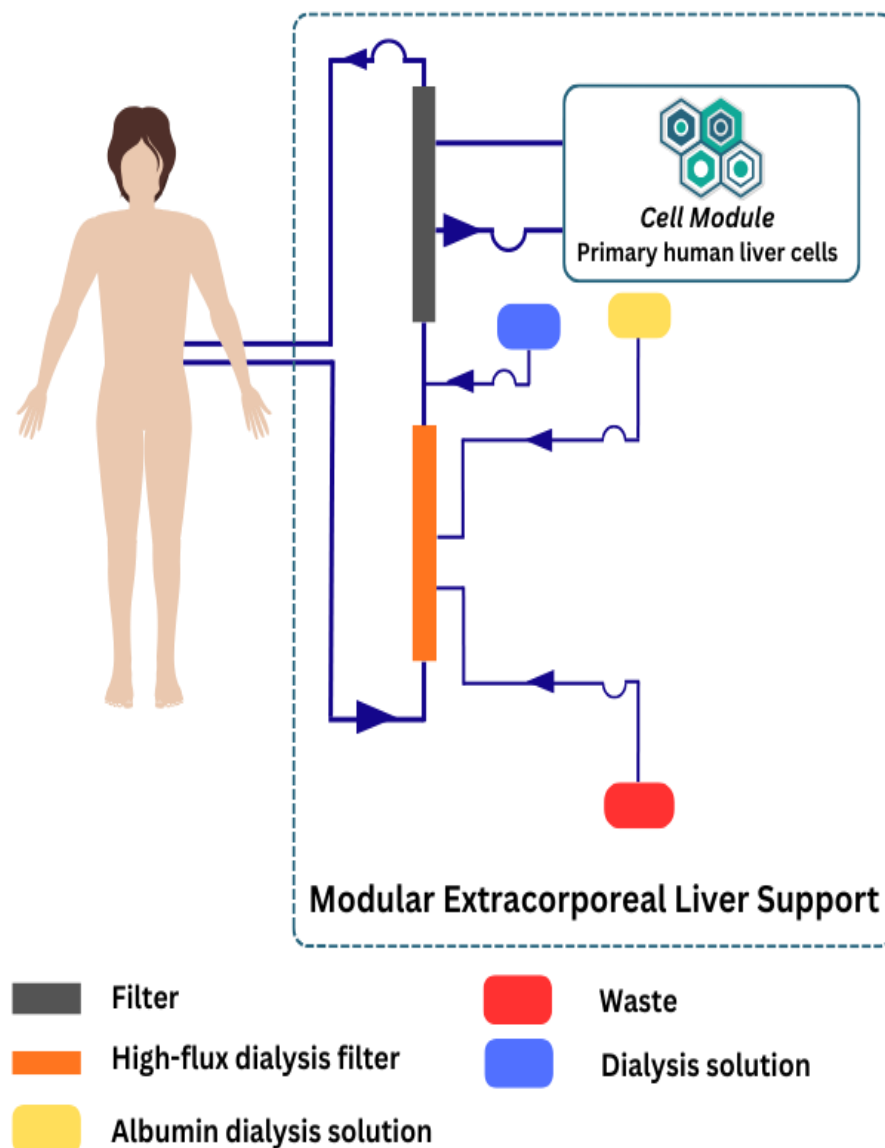
The patient's blood circulates through a circuit containing a high-flux hollow fiber hemodiafilter (Fresenius HdF 100S, polysulfone high-flux hemodiafilter, Fresenius AG, Bad Homburg). The opposite side of the membrane is perfused with an albumin-containing solution, flowing counter-currently and discarded after passing through the filter. A standard 4.5-liter dialysis buffer solution bag is replaced with 1000 ml of 20% human albumin solution, resulting in a final albumin concentration of 4.4%. During therapy, the blood pump rate is adjusted to 130–180 ml/min, and the dialysis pump rate to 600 ml/hour.

Because 30–75% of ALF patients exhibit renal failure characterized by fluid overload, electrolyte disturbances, and elevated creatinine levels, the MELS concept integrates continuous renal



replacement therapy (CRRT) through high-flux hollow fiber hemodiafiltration as part of the DetoxModule. Standard buffered aqueous solutions are used (“post-dilution,” added after the filter) at flow rates of 1000–3000 ml/hour.

For a practical summary of our review, including comparative indications, mechanisms, benefits, and limitations, see Table 2.



**Figure 2.** Schematic Diagram of Bioartificial Liver

**Table 2.** Comparative summary of major extracorporeal liver support systems

| Modality   | Indications                                                                                                                                                                                                                                                                                       | Mechanism                                           | Benefits                                                                                                                                                                                                                                                                                                                                                          | Limitations                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| MARS       | Decompensated CLD, ALF <sup>8</sup> , AoCLF <sup>9</sup> , bridge to liver transplantation, postoperative liver insufficiency <sup>10</sup> , severe cholestasis with refractory pruritus <sup>8</sup> , cardiopulmonary failure on ECMO <sup>11</sup> , drug-induced liver failure <sup>12</sup> | Albumin-based recirculating dialysis + hemodialysis | <ul style="list-style-type: none"> <li>Removes albumin-bound &amp; water-soluble toxins</li> <li>Key mediator of systemic effects in liver failure</li> <li>Reduction of oxidative stress</li> <li>Useful for intoxications with protein-bound drugs</li> <li>Improve hepatic encephalopathy and renal function in liver failure patients<sup>13</sup></li> </ul> | <ul style="list-style-type: none"> <li>Bridging/supportive therapy only</li> <li>No proven survival benefit; long-term outcomes remain limited<sup>2,14</sup></li> <li>Depend on the timing of intervention and patient selection<sup>2,14</sup></li> <li>High cost; technically complex, limited accessibility in developing country</li> <li>Adverse events: thrombocytopenia, electrolyte disturbances, and worsening coagulopathy<sup>15,16</sup></li> </ul> |
| SPAD       | Mainly ALF <sup>17</sup> , bridge to transplant, AoCLF, hepatorenal syndrome <sup>17</sup>                                                                                                                                                                                                        | Single-pass albumin dialysis via CRRT system        | <ul style="list-style-type: none"> <li>Removes albumin-bound &amp; water-soluble toxin</li> <li>High efficiency in detoxification</li> <li>Cost-effective, simple to implement</li> <li>Widely accessible in ICU</li> </ul>                                                                                                                                       | <ul style="list-style-type: none"> <li>Bridging/supportive therapy only</li> <li>High albumin consumption</li> <li>Potential for electrolyte and metabolic disturbances (when using regional citrate anticoagulation)<sup>18</sup></li> </ul>                                                                                                                                                                                                                    |
| Prometheus | ALF, AoCLF, acute alcoholic hepatitis, hepatorenal syndrome, hepatic encephalopathy, and its use as a bridging therapy to liver transplantation                                                                                                                                                   | Fractionated plasma separation + adsorption         | <ul style="list-style-type: none"> <li>Remove both albumin-bound and water-soluble toxins</li> <li>Removes both conjugated &amp; unconjugated bilirubin, bile acids,</li> </ul>                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>High rates of ammonia production or redistribution<sup>7</sup></li> <li>No significant effect on cytokines, coagulation factors, or plasma proteins<sup>19</sup></li> <li>Alters the bile acid profile towards</li> </ul>                                                                                                                                                                                                 |

|       |                                                                                                 |                                                                                       |                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                   |
|-------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|       |                                                                                                 | pruritus due to cholestasis and intoxication with protein-bound drugs <sup>7,19</sup> | creatinine, urea <sup>7</sup> <ul style="list-style-type: none"><li>• More accessible and can be more easily implemented in a wider range of clinical settings</li></ul>                                                                                           | more hydrophobic bile acids, which could potentially be harmful <sup>20</sup> <ul style="list-style-type: none"><li>• Unintended loss of endogenous albumin</li><li>• Adverse event: high risk of bleeding</li></ul>                                                                                                                              |
| ADVOS | AoCLF with multi-organ failure, hypoxic liver injury, AKI, cardiogenic shock, ARDS <sup>4</sup> | Albumin dialysis with dialysate pH modulation                                         | <ul style="list-style-type: none"><li>• Eliminating both water-soluble and albumin-bound substances</li><li>• Individualized acid–base correction, improves pH &amp; CO<sub>2</sub><sup>21</sup></li><li>• Improving hemodynamic parameters<sup>21</sup></li></ul> | <ul style="list-style-type: none"><li>• Requires specialized equipment and trained personnel, which may limit its availability and increase healthcare costs</li><li>• Uncertain long-term efficacy and survival benefits</li></ul>                                                                                                               |
| BAL   | ALF, bridge to transplant/recovery                                                              | Hepatocyte bioreactor + dialysis                                                      | <ul style="list-style-type: none"><li>• Provide both detoxification and synthetic functions<sup>22</sup></li><li>• BALs may allow for sufficient liver regeneration, potentially eliminating the need for a transplant</li></ul>                                   | <ul style="list-style-type: none"><li>• High cost and complexity of procedures</li><li>• Limited availability of high-quality human hepatocytes and the difficulty in maintaining their function over time<sup>22,23</sup></li><li>• Issues like mass transfer, immunobarriers, and bioreactor design need to be optimized<sup>23</sup></li></ul> |

MARS = Molecular Adsorbent Recirculating System; CLD = Chronic Liver Disease; ALF = Acute Liver Failure; AoCLF = Acute on Chronic Liver Failure; ECMO = Extracorporeal Membrane Oxygenation; SPAD = Single Pass Albumin Dialysis; CRRT = Continuous Renal Replacement Therapy; ICU = Intensive Care Unit; ADVOS = Advanced Organ Support; BAL = Bioartificial Liver Support

## CONCLUSION

Technological advancements in intensive care have led to the development of various extracorporeal liver support systems that provide vital support for patients with acute and chronic liver failure. Systems such as MARS, SPAD, Prometheus, ADVOS, and bioartificial liver devices play a crucial role in stabilizing clinical conditions, improving organ dysfunction, and serving as a bridging therapy toward liver transplantation or spontaneous hepatic recovery.

MARS and SPAD have demonstrated efficacy in removing albumin-bound toxins, while Prometheus introduces a fractional separation technique for dual-mode detoxification. ADVOS offers flexibility in acid-base correction, and bioartificial liver systems provide metabolic support that mimics physiological hepatic function. However, to date, no single system has consistently been shown to improve long-term survival in large-scale clinical trials.

The selection of an appropriate liver support system should be individualized based on the patient's clinical condition, therapeutic goals, infrastructure, and availability of

technology within the healthcare facility.

A multidisciplinary approach involving anesthesiologists, intensivists, hepatologists, and nephrologists is essential to optimize treatment outcomes. Looking ahead, the development of more physiological, efficient, and cost-effective systems remains both a challenge and a hope in addressing the current limitations of liver failure therapies. In accordance with this article, several gaps remain regarding the optimal use of extracorporeal liver support, including when to initiate treatment, which patient subgroups are most likely to benefit from each modality, and whether any approach confers a consistent survival advantage. Rigorous economic evaluations are also needed to establish cost-effectiveness and to define clear, context-specific indications for adoption in routine care. Accordingly, future research should prioritize adequately powered multicenter studies with extended follow-up, standardized protocols, and patient-centered endpoints that capture long-term efficacy, transplant-free survival, health-related quality of life, and the integration of these technologies into evidence-based management algorithms.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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