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# Artificial liver: Perspective of biomedical engineering

# Hígado artificial: Perspectiva de ingeniería biomédica

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**Abstract**

*Liver failure remains a critical condition with limited therapeutic options beyond transplantation. The growing demand for alternatives has driven the development of artificial liver support systems (ALS), aimed at emulating essential liver functions. This review addresses the main technological approaches: artificial, bioartificial, and hybrid devices, highlighting their detoxification and metabolic support mechanisms. Key aspects of engineering design are analyzed, such as bioreactor architecture, selection of biocompatible biomaterials, microfluidic dynamics, and 3D bioprinting. Furthermore, the integration of artificial intelligence for real-time monitoring, anatomical modeling, and predictive control is examined. Stem cell-derived liver organoids are presented as emerging platforms for regenerative applications. From a critical perspective, the clinical role of ALS in acute and chronic liver failure is evaluated, as well as its use as a bridge to transplantation. Finally, pending challenges in immunocompatibility, vascularization, and scalability are identified. The future of liver support points to a convergence of engineering, regenerative biology, and artificial intelligence, with the potential to transform personalized liver medicine.*

**Keywords:** artificial liver; bioartificial liver; liver organoids; 3D bioprinting; tissue engineering.

**Resumen**

*La insuficiencia hepática continúa siendo una condición crítica con opciones terapéuticas limitadas más allá del trasplante. La creciente demanda de alternativas ha impulsado el desarrollo de sistemas artificiales de soporte hepático (SAHE), orientados a emular funciones esenciales del hígado. Esta revisión aborda los principales enfoques tecnológicos: dispositivos artificiales, bioartificiales e híbridos, destacando sus mecanismos de desintoxicación y soporte metabólico. Se analizan aspectos clave del diseño ingenieril, como la arquitectura del biorreactor, la selección de biomateriales biocompatibles, la dinámica microfluídica y la bioimpresión 3D. Además, se examina la integración de inteligencia artificial para el monitoreo en tiempo real, modelado anatómico y control predictivo. Los organoides hepáticos derivados de células madre se presentan como plataformas emergentes para aplicaciones regenerativas. Desde una perspectiva crítica, se evalúa el papel clínico de los SAHE en insuficiencia hepática aguda y crónica, así como su uso como puente al trasplante. Finalmente, se identifican desafíos pendientes en inmunocompatibilidad, vascularización y escalabilidad. El futuro del soporte hepático apunta hacia una convergencia entre ingeniería, biología regenerativa e inteligencia artificial, con potencial para transformar la medicina hepática personalizada.*

**Palabras clave**: hígado artificial; hígado bioartificial; organoides hepáticos; bioimpresión 3D; ingeniería de tejidos.

## 1 Introduction

Liver failure remains one of the principal causes of morbidity and mortality at the global level, contributing to over two million deaths annually, primarily as a result of the increasing incidence of both acute and chronic hepatic diseases such as viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD). These conditions are strongly associated with lifestyle modifications, exposure to hepatotoxic agents, and persistent viral infections (Gong *et al*., 2025; He *et al*., 2019). Despite the

liver's remarkable regenerative capacity, this ability becomes insufficient when extensive or repeated injury leads to structural collapse and functional compromise, particularly in advanced stages of hepatic failure (Li *et al*., 2019).

Currently, liver transplantation remains the gold standard for the treatment of irreversible hepatic failure. However, this intervention is severely constrained by a global shortage of organ donors, high financial costs, the risk of immune rejection, and the requirement for lifelong immunosuppression (Jasirwan *et al*., 2023). These limitations have prompted the search for alternative strategies, including the development of Artificial Liver Support Systems (ALSS), which are designed to provide temporary or adjunctive hepatic function until either native liver recovery or transplantation becomes viable.

ALSS technologies are generally classified into artificial, bioartificial, and hybrid systems. Artificial systems rely on physicochemical processes for detoxification, employing filters, adsorbents, and dialysis techniques to remove metabolic waste. In contrast, bioartificial systems integrate biological elements—typically primary hepatocytes or stem cell-derived hepatic cells—with synthetic scaffolds or bioreactors to emulate the metabolic and synthetic functions of the liver (Gadour, 2025; Ramli *et al*., 2020). Hybrid configurations combine these elements to enhance detoxification, protein synthesis, and immunoregulatory capabilities under dynamic, flow-controlled conditions (Rondón *et al*., 2025).

Advances have profoundly influenced the evolution of ALSS in biomedical engineering. Innovations in material science, microscale fluid dynamics, and bioreactor engineering have enabled the development of implantable hepatic devices, patient-specific hepatic constructs fabricated via 3D printing, and organ-on-chip platforms that emulate hepatic microenvironments with high fidelity (Bhardwaj *et al*., 2024). Additionally, integrating artificial intelligence (AI) into liver support systems has allowed for predictive modeling of hepatic function, real-time monitoring of disease progression, and adaptive optimization of system performance (Jumaah *et al*., 2025).

Recent breakthroughs in hepatic tissue engineering have highlighted the utility of liver organoids derived from human pluripotent stem cells. These self-organizing microstructures reproduce essential aspects of hepatic architecture and function *in vitro* and are increasingly applied in high-throughput pharmacological testing and pathophysiological modeling. Moreover, they show promise as bioactive modules in future bioartificial liver systems (Akhtar, 2024).

In light of the liver's multifaceted physiological roles and the urgent need for therapeutic alternatives to transplantation, ALSS development represents both a technological challenge and a translational opportunity. This article comprehensively overviews current and emerging technologies in artificial liver engineering. It emphasizes engineering approaches, regenerative platforms, integration with AI systems, and persisting translational barriers. The objective is to delineate current research gaps and propose strategic directions to enhance clinical applicability and improve patient outcomes.

## 2 Methodology

- *Search and data compilation:* A comprehensive literature search was conducted using databases including PubMed, ScienceDirect, IEEE Xplore, Springer, MDPI, ResearchGate, and Frontiers. Search terms included "artificial liver", "bioartificial liver", "liver organoids", "3D bioprinting", "hepatocyte bioreactor", "AI in regenerative medicine", and "tissue engineering for hepatic systems". The search covered peer-reviewed publications from 1995 to 2025.
- *Information selection and refinement:* Retrieved articles were screened for relevance, focusing on works that provide experimental, clinical, or technological insights into the development and application of ALSS. Mendeley was used for reference organization. Key selection criteria included novelty, translational potential, and scientific rigor (see Figure 1).
- *Thematic structuring:* Selected works were classified into core thematic areas: (a) classification of ALSS, (b) engineering design and materials, (c) computational and AI modeling, (d) organoids and regenerative liver systems, and (e) clinical trials and implementation barriers.

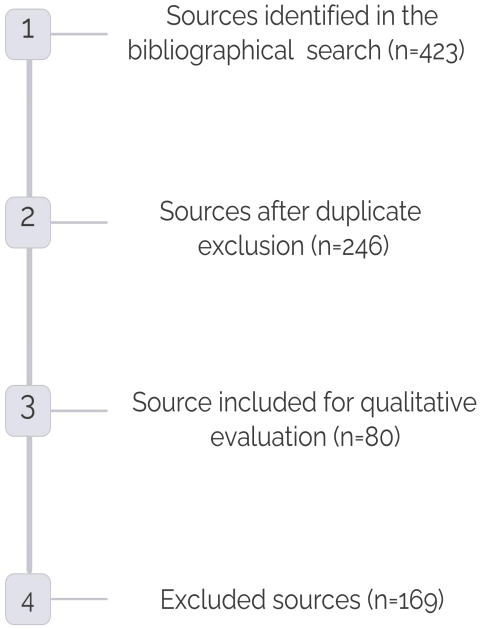

**Figure 1**. Flowchart of the study selection methodology for this research.

- *Critical analysis:* Cross-comparative analyses were performed to identify technological gaps, converging trends, and future research directions. Emphasis was placed on evidence-based evaluation of functionality, cell compatibility, and scalability for clinical translation (Jumaah *et al*., 2025; Akhtar, 2024; Rondón *et al*., 2024).

## 3 Results and discussion

### *3.1 Classification of artificial liver systems*

Artificial Liver Support Systems (ALSS) are generally classified into three main categories based on their mechanism of action, biological integration, and clinical purpose: (1) purely artificial systems, (2) bioartificial systems, and (3) hybrid systems and Emerging Strategies (He *et al*., 2019; Jasirwan *et al*., 2023; Ocskay *et al*., 2021). This classification is fundamental for understanding the technological evolution of hepatic support strategies and their functional differentiation (Table 1).

1. *Artificial systems* rely on non-biological methods such as filtration, adsorption, and dialysis to eliminate endogenous and exogenous toxins from the bloodstream. The most prominent examples include the Molecular Adsorbent Recirculating System (MARS), Single-Pass Albumin Dialysis (SPAD), and Prometheus.

MARS combines albumin dialysis with conventional renal replacement therapy to eliminate protein-bound toxins and cytokines (Jasirwan *et al*., 2023; Sen *et al*., 2005; Papamichalis *et al*., 2023). However, these systems do not replicate hepatic metabolic or synthetic functions and are limited to providing temporary detoxification support.

Their clinical use is generally restricted to bridging patients with acute liver failure to transplantation or spontaneous recovery (Stange *et al*., 1999; Feng *et al*., 2024).

2. *Bioartificial systems* combine synthetic membranes with functional biological components, primarily hepatocytes, to perform metabolic and synthetic activities. Notable examples include HepatAssist, ELAD, and the Spheroid Reservoir Bioartificial Liver (SRBAL).

HepatAssist incorporates porcine hepatocytes within a hollow-fiber bioreactor, mimicking key hepatic functions such as ammonia detoxification, gluconeogenesis, and protein synthesis (Li *et al*., 2019; Ellis *et al*., 1996; Heydari *et al*., 2020).

ELAD, developed by Vital Therapies, uses human C3A hepatoblastoma cells to provide metabolic support in a similar extracorporeal configuration (Rondón e*t al*., 2025). While preclinical results have been promising, clinical trials have yielded mixed outcomes regarding efficacy and patient survival (Akhtar, 2024; Sánchez *et al*., 2014).

Although ALSS technologies represent a promising alternative for patients with liver failure, numerous clinical, logistical, and ethical barriers must still be addressed to ensure their safe, effective, and equitable integration into modern healthcare systems.

Ultimately, ALSS are poised to revolutionize the therapeutic landscape of hepatology. As these technologies evolve from extracorporeal support toward complete organ replacement, they hold the potential to extend life and restore both liver function and quality of life for patients worldwide.

Their clinical success would mark a transformative milestone in the era of personalized and regenerative hepatic medicine (Bhardwaj *et al*., 2024; Sommerfeld *et al*., 2023).

**Table 1.** Classification of artificial liver support systems

| System | Description | Advantages | Limitations |
|---|---|---|---|
| Artificial | Mechanical/chemical filtration is used to remove toxins. E.g., MARS, SPAD, Prometheus. | Rapid toxin clearance; well-established technology. | Does not replicate metabolic functions; it provides only temporary support. |
| Bioartificial | Combines synthetic components with living hepatocytes. E.g., HepatAssist, ELAD, SRBAL. | Offers metabolic and synthetic support; better functional mimicry. | Cell compatibility issues; variable clinical outcomes. |
| Hybrid | Integrates artificial detoxification modules (e.g., MARS) with cell-based bioreactors. | Synergistic detoxification + metabolism; broader clinical potential. | Technological complexity, challenges in immunocompatibility, and scalability. |

*3. Hybrid Systems and Emerging Strategies.* Hybrid systems incorporate advanced structural and functional approaches, such as cell encapsulation and immune-isolated scaffolds, to minimize host immune responses and improve long-term performance (Bhatt *et al*., 2024; García & Bendjelid, 2018). In parallel, emerging research is focusing on the use of hepatocyte-like cells derived from induced pluripotent stem cells (iPSCs), which offer a renewable and less immunogenic cellular source (Gong *et al*., 2025; Akhtar, 2024; Gao *et al*., 2020; Cerneckis *et al*., 2024)

In this context, computational modeling and artificial intelligence (AI) algorithms are increasingly used to simulate device performance and optimize detoxification rates, shear stress, and nutrient flow dynamics in real time (Jumaah *et al*., 2025).

*3.1.1 Limitations and translational challenges*

Despite their potential, current systems face critical limitations related to scalability, immunocompatibility, and the long-term viability of hepatocytes. Standardizing protocols and implementing multicenter clinical trials are essential steps for validating clinical efficacy and establishing regulatory pathways for approval (Ocskay *et al*., 2021; Sánchez *et al*., 2014; Joo *et al*., 2025).

*3.2 Engineering considerations and biomaterials*

Artificial Liver Support Systems (ALSS) 's successful development depends on applying engineering principles that ensure functional mimicry, biocompatibility, mechanical integrity, and effective cellular integration (Table 2). Key design parameters include bioreactor architecture, material properties, fluid dynamics, nutrient transport, and hepatocyte viability (Jasirwan *et al*., 2023; Gadour, 2025; Zhidu *et al*., 2024; Chehelgerdi *et al*., 2023).

*3.2.1 Bioreactor and device design*

Bioreactors in bioartificial liver systems are engineered to emulate hepatic perfusion and mass transport characteristics. Hollow fiber membrane bioreactors (HFMBs) remain the gold standard due to their high surface area-to-volume ratio, facilitating efficient exchange of oxygen, nutrients, and metabolic waste (Li *et al*., 2019; Lanza *et al*., 2020). Nonetheless, limitations such as shear stress-induced cellular damage and heterogeneous nutrient distribution persist. To address these issues, next-generation dynamic flow systems and microfluidic devices are being actively investigated (Barbosa *et al*., 2025; Gimondi *et al*., 2023).

*3.2.2 Biomaterial selection*

Biomaterials function as scaffolds and structural supports for hepatocyte adhesion and activity. Ideal materials must exhibit biocompatibility, non-immunogenicity, mechanical robustness, and support for cell proliferation and functionality (Rondón *et al*., 2025). Natural polymers such as alginate, gelatin, collagen, and chitosan offer inherent bioactivity and cell-binding motifs, although they often lack sufficient mechanical strength (Mogoşanu & Grumezescu, 2014). In contrast, synthetic polymers like polyethylene glycol (PEG), polylactic acid (PLA), and polycaprolactone (PCL) offer tunable mechanical properties and degradation rates, though surface modifications are often required to enhance cell compatibility (Trimukhe *et al*., 2017; Rondón *et al*., 2023).

*3.2.3 Surface modification techniques*

Surface modification techniques such as plasma surface modification (PSM) and chemical grafting are commonly employed to improve surface wettability and increase the availability of functional groups that promote protein adsorption and cell interaction (Karthik *et al*., 2023). Plasma-treated materials have enhanced hepatocyte attachment, spreading, and metabolic activity, especially when modified with amine or hydroxyl groups (Ma *et al*., 2018).

**Table 2.** Biomaterials used in artificial liver support systems (ALSS)

| Type of Material | Examples | Characteristics |
|---|---|---|
| Natural Polymers | Alginate, collagen, chitosan | High bioactivity, but limited mechanical strength. |
| Synthetic Polymers | PLA, PEG, PCL | Tunable mechanical properties and degradation rates often require surface functionalization. |
| Surface-Modified Materials | Plasma-treated surfaces, chemical grafting | Improve cell adhesion and hepatic activity through enhanced surface functionality. |

*3.2.4 Scaffold fabrication and 3D bioprinting*

The advent of three-dimensional bioprinting has enabled the fabrication of liver-mimetic architectures featuring vascular channels and controlled porosity, thereby improving oxygen diffusion and hepatocyte organization (Bhardwaj *et al*., 2024). Bioprinted constructs using bioinks derived from decellularized liver extracellular matrix (dECM) or stem cell-based formulations have improved liver-specific function and *in vitro* viability (Gong *et al*., 2025; Pruinelli *et al*., 2025).

*3.2.5 Cell source and compatibility*

Primary human hepatocytes remain the gold standard for replicating hepatic function. However, their limited availability and short *in vitro* lifespan pose significant challenges (He *et al*., 2019). As alternative sources, hepatocyte-like cells derived from induced pluripotent stem cells (iPSCs) or mesenchymal stem cells are being explored, as they can be expanded and differentiated under controlled conditions. Nevertheless, their long-term functionality remains under investigation (Akhtar, 2024; Rawashdeh, 2024).

Finally, the engineering of liver-on-chip platforms and implantable ALSS devices demands a multidisciplinary integration of materials science, tissue engineering, microfluidics, and biomedical computing. This convergence is essential to optimize functionality, ensure clinical safety, and enable scalable production.

*3.3 Artificial intelligence and anatomical modeling*

Each day, it becomes increasingly evident that artificial intelligence (AI) and computational modeling have become essential tools in developing next-generation artificial liver support systems. These technologies are crucial in device design, functional optimization, anatomical simulation, real-time control, and predictive diagnostics (Jumaah *et al*., 2025; Son *et al*., 2020) (Table 3).

**Table 3.** Applications of artificial intelligence (AI) in artificial liver support systems (ALSS)

| AI Application | Description |
|---|---|
| Functional Optimization | Adjustment of flow rates, cell metabolism, and toxin clearance using machine learning algorithms. |
| Predictive Modeling & Digital Twin | Personalized simulation of hepatic physiology and therapeutic response. |
| Medical Image Segmentation | Automatic reconstruction of liver geometries for surgical planning or 3D printing. |
| Support in Biofabrication | Automated design of bioprinted structures, including cell, bioink, and vascular channel placement. |
| Real-Time Control | Dynamic regulation of biochemical parameters via sensors and adaptive feedback systems. |

*3.3.1 AI-assisted functional optimization*

Machine learning algorithms have successfully enhanced key operational parameters in ALSS, including toxin elimination rates, flow dynamics, and cell viability. A representative example of this trend is the *Artificial Liver Classifier* (ALC), a bioinspired model that simulates hepatic detoxification logic using a feed-forward neural network architecture, achieving high classification accuracy and minimal overfitting (Jumaah *et al*., 2025). This approach demonstrates the potential of AI to replicate complex liver functions through *in silico* simulation and its efficient integration with hardware systems via adaptive feedback control.

*3.3.2 Predictive modeling and digital twin*

AI-enabled simulations have led to the development of liver digital twin models—virtual replicas that integrate patient-specific anatomical and physiological data. These models allow for simulation of disease progression, prediction of treatment response, and support for preoperative planning in bioartificial liver system integration (Wang *et al*., 2021; Tuerxun *et al*., 2022). Their utility is particularly relevant in intensive care units, where real-time physiological monitoring can guide immediate adjustments in ALSS therapy.

*3.3.3 Medical image segmentation and anatomical design*

Deep learning algorithms, such as convolutional neural networks (CNNs), are applied to medical imaging (MRI, CT) for the automated segmentation of hepatic structures (Ouchi & Koike, 2023; Liu *et al*., 2024). These procedures are fundamental for reconstructing personalized liver geometries used in surgical planning, scaffold design, or

organ-on-chip platforms. AI-assisted segmentation reduces manual workload and enhances the spatial resolution and accuracy of the resulting anatomical models.

*3.3.4 Integration with advanced biofabrication*

AI models have also been implemented to automate bioprinted design by predicting optimal deposition patterns for cells, bioinks, and vascular channels. When combined with computer-aided design (CAD) tools, these systems rapidly create hepatic constructs with spatially controlled architectures (Bhardwaj *et al*., 2024; Pruinelli *et al*., 2025). This integration represents a critical bridge between virtual modeling and physical biofabrication.

*3.3.5 Real-time feedback through biosensors*

It is important to highlight that the most advanced ALSS prototypes incorporate biosensors capable of monitoring key biochemical parameters—such as ammonia, urea, albumin, and glucose—in real time. AI algorithms analyze this data to dynamically regulate media flow, nutrient delivery, and cellular metabolism, creating a closed-loop control system (Takebe *et al*., 2013; Takebe *et al*., 2017). These adaptive platforms open new perspectives for developing next-generation wearable or implantable liver support devices.

*3.4 Bioactive additives*

Incorporating bioactive additives into injectable hydrogels has significantly improved their regenerative potential, particularly in applications targeting joint repair. These additives enhance the system's biological performance and confer therapeutic functions beyond mere structural support. In this context, hydrogels function as platforms for the controlled, localized, and sustained release of bioactive agents such as growth factors, anti-inflammatory compounds, and stem cells (Nguyen *et al*., 2024; Nguyen *et al*., 2017).

Among the most relevant signaling molecules are transforming growth factor-beta (TGF-β), bone morphogenetic protein-7 (BMP-7), and insulin-like growth factor-1 (IGF-1), all of which play fundamental roles in cartilage regeneration. These factors promote chondrocyte proliferation, extracellular matrix synthesis, and lineage-specific differentiation. When encapsulated within hydrogel matrices, they induce targeted therapeutic responses while minimizing systemic side effects. Preclinical models have shown that TGF-β-loaded hydrogels enhance the chondrogenic differentiation of mesenchymal stem cells (MSCs) and accelerate the deposition of cartilaginous matrix (Qin *et al*., 2023; Peng *et al*., 2019; Du *et al*., 2023; Mariani *et al*., 2014).

MSCs, widely used as cellular bioactive components, exhibit dual functionality in immunomodulation and differentiation. When integrated into biocompatible hydrogel matrices, these cells release trophic factors that attenuate inflammation, stimulate endogenous repair mechanisms, and integrate functionally into the surrounding cartilage matrix (Han *et al*., 2022; Zhang *et al*., 2022).

Recent advances have also led to the design of hydrogels with time-controlled or stimulus-responsive release properties. These innovative delivery systems use internal or external triggers—such as pH changes, temperature variations, or enzymatic activity—to activate the release of encapsulated agents, thereby optimizing therapeutic windows by the stages of tissue healing (Lu *et al*., 2024; Municoy *et al*., 2020; Ribeiro *et al*., 2024). In addition, dual-delivery hydrogels have been developed to mimic the spatial and temporal complexity of biochemical signaling involved in cartilage repair (Hashemi-Afzal *et al*., 2025).

Moreover, hydrogels have been engineered to deliver anti-inflammatory agents such as dexamethasone, curcumin, and interleukin-1 receptor antagonists (IL-1Ra) to modulate the inflammatory microenvironment characteristic of osteoarthritic joints. These compounds maintain tissue homeostasis and protect the regenerating cartilage from immune-mediated degradation (Nguyen *et al*., 2024; Nguyen *et al*., 2017).

In parallel, state-of-the-art bioactive hydrogels incorporate nanoscale design elements and extracellular matrix-mimetic components to enhance cell adhesion, retention, and viability. Specifically, the incorporation of matrix metalloproteinase (MMP)-sensitive linkers allows for degradation synchronized with local tissue remodeling processes, supporting adaptive, patient-specific therapies (Lu *et al*., 2024; Cabral-Pacheco *et al*., 2020; Gonzalez-Avila *et al*., 2019).

Nevertheless, several translational hurdles remain. Significant challenges include achieving uniform spatial distribution of bioactive additives, preventing premature system degradation, ensuring production scalability, and standardizing release profiles across diverse patient populations. Overcoming these limitations will require close collaboration among biomedical engineers, materials scientists, and clinical professionals focused on refining hydrogel architecture and enhancing the precision of therapeutic delivery.

*3.5 Organoids and regenerative medicine*

Today, the emergence of liver organoids has redefined the landscape of regenerative medicine by enabling the development of three-dimensional biomimetic microstructures capable of reproducing liver-specific functions under *in vitro* conditions (Gong *et al*., 2025). These organoids, derived from pluripotent stem cells (PSCs), adult stem cells (ASCs), or hepatic progenitors, possess the ability to self-organize into spheroidal or lobule-like structures that emulate key features of liver architecture

and function, including drug metabolism, protein synthesis, and bile secretion (Luo *et al*., 2023).

### *3.5.1 Development and culture of liver organoids*

Liver organoids are commonly generated from embryonic stem cells (ESCs) and human-induced pluripotent stem cells (hiPSCs), typically cultured in three-dimensional matrices such as Matrigel, gelatin-methacrylate (GelMA), or decellularized extracellular matrix (dECM), which provide essential structural and biochemical cues (Ouchi & Koike, 2023; Hu *et al*., 2024).

Differentiation protocols involve the sequential administration of growth factors such as activin A, fibroblast growth factor (FGF), and hepatocyte growth factor (HGF), which promote the acquisition of functional hepatic phenotypes (Yang *et al*., 2022; Baddal & Mammadov, 2024).

### *3.5.2 Applications in drug testing and disease modeling*

Liver organoids represent a versatile platform for high-throughput hepatotoxicity testing and disease modeling. They have been successfully employed in the study of inherited liver diseases, viral hepatitis, and hepatic fibrosis, allowing for precise evaluation of drug–gene interactions in personalized contexts (Sorrentino *et al*., 2020; Nuciforo & Heim, 2021; Liu *et al*., 2024).

### *3.5.3 Integration into bioartificial systems*

Recent advances have focused on the integration of liver organoids with microfluidic systems and perfusable scaffolds, giving rise to "liver-on-a-chip" platforms that optimize nutrient exchange, prolong cell viability, and replicate mechanical stimuli present *in vivo* (Arroyo *et al*., 2020; Girish *et al*., 2025). When incorporated into Artificial Liver Support Systems (ALSS), organoids can function as active living units within bioreactors, enhancing synthetic performance and reducing reliance on animal-derived hepatocytes.

### *3.5.4 Current limitations*

Despite the progress achieved, significant technical challenges persist. These include batch-to-batch variability, incomplete hepatic zonation, absence of functional vascularization, and immune incompatibility in allogeneic applications (Xu *et al*., 2020; Kim *et al*., 2024). Additionally, derived hepatocytes frequently exhibit embryonic rather than adult phenotypes, limiting their metabolic capacity and reliability as functional models (Gong *et al*., 2025; Liu *et al*., 2024).

A critical limitation is the lack of a functional vascular network, which restricts efficient oxygen and nutrient diffusion, compromising tissue viability and long-term *in vitro* performance (Ouchi & Koike, 2023; Luo *et al*., 2023). This issue becomes particularly relevant when considering system scalability and translational applicability. Moreover, in allogeneic or xenogeneic contexts, immunogenicity remains a substantial barrier, necessitating the development of complementary strategies such as cell encapsulation, immune-isolated microenvironments, or targeted immunosuppressive protocols (Kim *et al*., 2024; Xu *et al*., 2020).

### *3.5.5 Future perspectives*

The clinical consolidation of liver organoids will require overcoming these limitations through advanced co-culture strategies involving endothelial, immune, or stromal cells, as well as the implementation of vascularized scaffolds and *in vivo* conditioning protocols that more accurately replicate physiological hepatic architecture and function (Gong *et al*., 2025; Liu *et al*., 2024).

From a biomedical engineering perspective, implementing liver organoids as bioactive platforms within hybrid liver support systems will demand the precise integration of biotechnological strategies, adaptive biomaterials, and intelligent bioelectronic interfaces. It is possible only through this convergence to achieve the compatibility, stability, and therapeutic efficacy required in real clinical scenarios.

### *3.6 Clinical applications and challenges*

Artificial Liver Support Systems (ALSS) have made significant progress from preclinical research, with clinical applications ranging from managing acute liver failure (ALF) to bridging therapy for liver transplantation.

However, transitioning from experimental prototypes to standardized clinical devices faces substantial regulatory, biological, and technological challenges (Jasirwan *et al*., 2023; Gadour, 2025; Brown *et al*., 2025).

### *3.6.1 Management of acute liver failure (ALF)*

In this critical condition, ALSS devices such as MARS and Prometheus have proven effective in stabilizing patients by removing neurotoxic substances like ammonia and bilirubin, thereby reducing hepatic encephalopathy and supporting hemodynamic stability (Sen *et al*., 2005; Papamichalis *et al*., 2023; Stange *et al*., 1999; Feng *et al*., 2024).

For instance, in a cohort of 113 ALF patients, MARS treatment achieved a one-year survival rate of 74%, which increased to 91% when liver transplantation was included (Sakiyama *et al*., 2017).

Nevertheless, their long-term impact on liver regeneration remains limited, and outcomes often depend on early intervention and appropriate patient selection (Thorgersen *et al*., 2019).

*3.6.2. Bridge to liver transplantation*

Bioartificial systems such as ELAD and HepatAssist have been used to prolong survival in patients on the transplant waiting list, improving their clinical status before transplantation. Despite the promise shown, randomized clinical trials have yielded mixed results, and definitive data on long-term efficacy are still lacking (Ellis *et al*., 1996; Heydari *et al*., 2020; Sánchez *et al*., 2014; Liu *et al*., 2022; Pless, 2007; Gerth *et al*., 2017).

*3.6.3. Chronic liver disease and acute-on-chronic liver failure (ACLF).*

Emerging evidence suggests that ALSS may also be beneficial in episodes of acute decompensation of chronic liver disease, reducing short-term mortality. MARS-based studies have shown significant mortality reductions in ACLF patients, although the benefit appears transient (Pless, 2007; Gerth *et al*., 2017). Advances in personalized device design may broaden their use in cirrhotic patients experiencing sudden deterioration (Yarrarapu & Sanghavi, 2025; Mielnicki *et al*., 2019).

*3.6.4. Regulation and safety*

One of the most critical challenges is the lack of unified regulatory standards. Issues such as immune compatibility, endotoxin leakage, thrombogenicity, and long-term biocompatibility remain unresolved. Furthermore, the heterogeneity in cell sources and device configurations hinders cross-study comparisons and delays regulatory approval by agencies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) (Gadour, 2025; Rondón *et al*., 2025; Joo *et al*., 2025).

*3.6.5. Cost, infrastructure, and accessibility*

High costs, complex technical requirements, and the need for multidisciplinary teams hinder the routine implementation of ALSS. In resource-limited settings, the infrastructure needed to sustain continuous extracorporeal support poses a significant barrier (Bañares *et al*., 2013; Saliba *et al*., 2022).

*3.6.6. Ethical and logistical challenges in organ replacement therapies*

With advances in hepatic organoids and implantable systems, ethical debates surrounding stem cell sourcing, genetic manipulation, and equitable access to advanced therapies are intensifying. It is imperative to develop global guidelines to govern these aspects for responsible implementation (Ballester *et al*., 2025; Riva *et al*., 2024; Hassanein *et al*., 2011).

## 5 Conclusion

Artificial Liver Support Systems (ALSS) represent a strategic convergence of biomedical engineering, tissue regeneration, stem cell biotechnology, and computational intelligence to address the growing global burden of liver failure. With over two million deaths annually attributed to hepatic dysfunction, the pursuit of viable alternatives to transplantation has driven the development of extracorporeal detoxification platforms, hepatocyte-based bioreactors, and regenerative technologies such as liver organoids.

This review has provided an integrative synthesis of ALSS technologies, highlighting their classification into artificial, bioartificial, and hybrid modalities, and analyzing the engineering principles, biological interfaces, and computational tools that support their development. Advancements in bioreactor design, microfluidic integration, and biomaterial functionalization have progressively enhanced cell viability and *in vitro* metabolic performance. Simultaneously, the rise of stem cell-derived liver organoids and 3D bioprinting has expanded the scope of regenerative hepatology, enabling disease modeling, pharmacological testing, and the potential creation of personalized autologous grafts.

Equally relevant has been the incorporation of artificial intelligence into real-time biosensor monitoring, the generation of digital twin models, and the adaptive control of hepatic devices, laying the foundation for predictive and personalized liver support. These emerging systems respond dynamically to physiological changes and can be algorithmically optimized according to individual patient needs.

Nevertheless, critical barriers remain. Limitations in immunocompatibility, reliability of cell sources, vascularization, and large-scale implementation continue to delay clinical translation. In addition, the absence of standardized regulatory frameworks and the ethical complexities associated with cellular manipulation and equitable access must be proactively addressed. Future success in this field will depend on the development of fully

vascularized, immunoprotected, and AI-integrated implantable liver constructs. Strategic alliances between academic institutions, biotechnology companies, and regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) will be essential to validate these systems at scale and ensure their bioethical deployment.

Thus, ALSS has transcended theoretical concepts to become active biomedical platforms with the potential to redefine hepatology. As they evolve from extracorporeal support systems to functional organ replacements, they hold unprecedented capacity to prolong life, restore liver function, and improve the quality of life for patients worldwide. Their successful integration will mark a pivotal transition toward personalized and regenerative hepatic medicine.

## 6 Recommendations

To consolidate the development and clinical implementation of Artificial Liver Support Systems (ALSS), it is essential to establish standardized international regulatory frameworks incorporating technical, biological, and ethical criteria. Such frameworks would enable cross-platform comparisons and facilitate approval by agencies like the FDA and EMA. Likewise, it is recommended to intensify research into hybrid systems that integrate detoxification modules with immunoisolated cellular components, thereby minimizing adverse responses in clinical applications. Engineering hepatic organoids requires clear prioritization of functional vascularization, a sine qua non condition for their integration into implantable devices or microfluidic platforms such as liver-on-a-chip. At the engineering design level, it is imperative to systematically apply artificial intelligence and computational modeling to develop bioreactors, optimizing critical parameters such as shear stress, nutrient diffusion, and toxin clearance kinetics.

In the field of biofabrication, it is essential to consolidate smart bioinks functionalized with growth factors and stimuli-responsive materials that enable stable and functionally active three-dimensional personalized bioprinting. In parallel, developing predictive models and hepatic digital twins that integrate anatomical, physiological, and molecular variables will allow for data-driven, real-time personalized support medicine. This entire technological ecosystem must be supported by multidisciplinary consortia composed of universities, research centers, biotech startups, and regulatory agencies to ensure the scalability, clinical validation, and global accessibility of ALSS.

Additionally, it is recommended that multicenter clinical trials be designed with an adaptive approach, considering the etiological heterogeneity of liver failure and incorporating biomarkers and genetic profiles as predictive variables. Finally, in light of the emerging use of stem cells, gene editing, and implantable devices, there is an urgent need to establish global bioethical guidelines that regulate their application, ensure patient privacy, and promote equitable access to these disruptive technologies.

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