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REVIEW ARTICLE

Selection Criteria for Liver Transplantation and Bridge Therapeutic Modalities in Acute Liver Failure

Daniel Medina Dias[1], Dulce Diogo[1,2,*], João Madaleno[1,2,3], José Guilherme Tralhão[1,2]

1.Universidade de Coimbra – Faculdade de Medicina – Coimbra – Portugal. 2.Centro Hospitalar e Universitário de Coimbra – Unidade de Transplantação Hepática de Adultos – Coimbra – Portugal. 3.Centro Hospitalar e Universitário de Coimbra – Serviço de Medicina Interna – Coimbra – Portugal.

*Correspondence author: dulce.diogo@chuc.min-saude.pt

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ABSTRACT

Introduction: Acute liver failure (ALF) is a condition that can rapidly progress to multiorgan failure. Therefore, different extracorporeal liver support systems have been developed to function as a *bridge* to transplantation or spontaneous survival. Conversely, the shortage of organs demands a rigorous selection process to determine whom should receive transplantation and several prognostic models have been proposed to identify the patients who would benefit the most from liver transplantation (LT). **Objectives**: A review of the main selection criteria used for LT in ALF is carried out, focusing mostly on the new proposed prognostic markers, and aiming to identify poor prognosis criteria associated with futility in LT. Extracorporeal liver support systems (ECLS) were also reviewed, including an analysis of their impact on the survival of patients with ALF. **Methods**: MEDLINE and PubMed databases were searched between 16th October 2021 and 5th December 2021. The inclusion criteria were: adult patients; patients with acute liver injury (ALI) or ALF; observational studies; clinical studies; case series; case-control studies; systematic reviews; meta-analysis. **Discussion:** King's College criteria (KCC) have been widely used and despite good specificity, have low sensitivity. Several markers have been used to improve prognostic accuracy, but the results are not sufficiently clear. Patient age, ABO incompatibility, and poor-quality grafting were potential factors that could indicate potential futility in LT. ECLS have a positive influence in clinical and laboratory parameters; however, there is no clear evidence of improvement in survival. **Conclusion**: ALF is a heterogeneous syndrome, which brings into question of the studies carried out to evaluate prognostic criteria to select patients for LT. It also narrows down the studies performed to evaluate the impact of ECLS on survival.

Descriptors: Acute Liver Failure; Liver Transplantation; Prognosis; Extracorporeal Life Support.

Critérios de Seleção para Transplantação Hepática e Modalidades Terapêuticas como Ponte na Falência Hepática Aguda

RESUMO

Introdução: A escassez de órgãos para transplantação hepática impõe uma seleção criteriosa dos doentes com falência hepática aguda. Vários modelos de prognóstico foram desenvolvidos para selecionar os doentes para transplantação. Essa síndrome pode evoluir rapidamente para falência multiorgânica. Assim, vários sistemas de suporte hepático extracorporal foram aperfeiçoados, com o objetivo de fazer a *ponte* para transplantação ou assegurar a recuperação do doente. **Objetivos**: Rever os principais critérios de seleção para transplantação hepática nos doentes com falência hepática aguda, incidindo sobretudo sobre os novos marcadores. Identificar os critérios de mau prognóstico associados a futilidade terapêutica. Rever os principais sistemas de suporte hepático extracorporal, analisando o seu impacto na sobrevida dos doentes com falência hepática aguda. **Métodos**: A pesquisa foi realizada na MEDLINE e Pubmed entre 16 de outubro de 2021 e 5 de dezembro de 2021. Os critérios de inclusão foram: doentes adultos; doentes com lesão hepática aguda ou falência hepática aguda; estudos observacionais; estudos clínicos; séries de casos clínicos; estudos caso-controlo; revisões sistemáticas; meta-análises. **Discussão**: Os critérios

de King's College têm sido amplamente utilizados. No entanto, apesar de boa especificidade, apresentam sensibilidade reduzida. Vários marcadores foram utilizados para melhorar a sua acuidade prognóstica, mas sem resultados claros até ao momento. Vários estudos apontaram a idade do doente, a incompatibilidade ABO e má qualidade do enxerto como potenciais fatores para futilidade terapêutica. Os sistemas de suporte hepático extracorporal têm influência positiva nos parâmetros clínicos e laboratoriais; no entanto, não demonstram claro aumento da sobrevida desses doentes. **Conclusão**: Este estudo permite concluir que a falência hepática aguda é uma síndrome heterogénea, o que prejudica a qualidade dos estudos efetuados para avaliar o impacto dos critérios de prognóstico na sobrevida dos doentes com falência hepática aguda, mas também tem limitado os estudos efetuados para avaliar o impacto dos sistemas de suporte hepático extracorporal na sobrevida.

Descritores: Falência Hepática Aguda; Transplante de Fígado; Prognóstico; Suporte Vital Extracorpóreo.

INTRODUCTION

Acute liver failure (ALF) is a rare condition characterized by an acute liver function impairment in patients without an underlying chronic liver disease, and manifests with jaundice, coagulopathy and altered level of consciousness.[1] Hepatic encephalopathy (HE) is an important clinical feature in defining ALF. Acute liver injury (ALI) is characterized by altered coagulation parameters without HE, and patients can progress to ALF. ALF can affect almost all organ systems, and is often associated with multiple organ dysfunction, and it may evolve to multiple organ failure (MOF).[2]

In developed countries, the five most common aetiologies of ALF are acetaminophen toxicity, ischaemia, drug-induced liver injury (DILI), hepatitis B virus (HBV) infection, and autoimmune dysfunction. In contrast, in developing countries the most common aetiologies of ALF are viral hepatitis A, B, and E. There are also three causes of ALF which represent a decompensation of chronic liver disease: Wilson's disease, reactivation of chronic HBV infection, and autoimmunity. Hyperacute ALF is mainly caused by acetaminophen toxicity and ischaemia. It is associated with very high levels of aminotransferases, and lower bilirubin concentrations, whereas slow evolving liver injuries (acute and subacute forms of ALF) are often caused by HBV infection, autoimmunity, or DILI. It is associated with lower aminotransferases concentrations, and higher levels of bilirubin. Overall, patients with hyperacute ALF have better short-term survival rates than patients with acute and subacute ALF.[2]

Liver transplantation (LT) is the only therapeutic available which effectively increases overall survival; however, its effectiveness was not clearly validated in randomized controlled trials. Before the era of LT, overall mortality of ALF was about 80-85%.[3] Germani *et al.* found that mortality decreased significantly with the widespread availability of LT. In this study, 1, 5 and 10-year survival rates were 74, 68, and 63%, respectively. Early post-LT mortality in ALF patients exceeds that of patients who receive LT for cirrhosis, reflecting the severity of ALF, with the majority of that (86%) occurring in the first 3 months.[3] However, LT is a limited resource and the decision to perform LT should be made carefully, because of the lack of organ donor availability, the risk of inappropriate LT, and the risks of immunosuppression. Since ALF can rapidly progress to MOF, it is crucial to assess prognosis of patients, differentiating those who will recover spontaneously from those who will not survive without LT. Accurate prognostic indices have been a focus of many investigations but are still lacking and in 2017, the European Association for the Study of the Liver presented new guidelines on the management of ALF, addressing the lack of uniformity in the criteria used to assess prognosis.[1]

Considering the risks of LT, different alternatives have been studied to support liver regeneration as a *bridge* modality, either while waiting for a suitable organ for LT or as a *bridge* modality to liver regeneration.[4] In ALF, hepatocellular dysfunction leads to the accumulation of serum toxins, such as ammonia, proinflammatory cytokines, and aromatic amino acids, contributing to the development of HE and MOF. Water-soluble metabolites can be removed from the blood using renal replacement therapies; however, hydrophobic and albumin-binding metabolites cannot be removed using these techniques.[5] Extracorporeal liver support systems (ECLS) are extracorporeal devices that mimic the three primary hepatic functions: (1) detoxification of damaging toxins; (2) biosynthesis (e.g., albumin and coagulation factors); and (3) regulation of normal serum biochemistry. There are two groups of ECLS: artificial and bioartificial (or cell-based).[5]

In this study, a review of the most important criteria used to select ALF patients for LT is proposed, as well as their strengths and weaknesses, and how the accuracy of these prognostic models can be improved. Furthermore, the scope of this review includes identifying criteria of poor prognosis post-LT which can anticipate futile LT. This study also aims to review the most relevant studies which used ECLS devices, focusing on their potential role in improving mortality and morbidity of ALF patients.

METHODS

The MEDLINE and PubMed databases were used between 16th October 2021 and 5th December 2021 to search for articles on two subjects (1) prognostic models and its impact on ALF; and (2) ECLS systems and its impact on ALF. For the prognostic models, the medical subject headings (MeSH) terms *Acute Liver Failure* OR *Liver Transplantation* were mainly used in combination with other free text terms, such as *Prognosis* OR *Prognostic* OR *Survival* OR *Outcome*, which were the basis of this research. These terms were also combined with others to refine the results, such as *King's College* OR *Kings College* OR *Clichy* OR *Lactate* OR *Phosphate* OR *Biomarkers* [MeSH] OR *MicroRNA*s [MeSH] OR *Acetaminophen* OR Paracetamol. For the ECLS systems search, the MeSH term *Acute Liver Failure* was mainly used, combined with other free text terms, such as *Extracorporeal Liver Support* OR *Extracorporeal Liver Device* OR *Liver Support*, which provided the basis for this research. These terms were also combined with others to refine the results, such as *Albumin Dialysis* OR *Molecular Adsorbent Recirculating System* OR *MARS* OR *Single-Pass Albumin Dialysis* OR *Plasma Exchange* OR *Fractionated Plasma Separation and Adsorption* OR *Prometheus*.

In this review, we considered the articles which included the following inclusion criteria: adult patients; patients with ALI or ALF; observational studies; clinical studies; case series; case-control studies; systematic reviews; meta-analysis. The following were excluded: paediatric patients; patients with acute-on-chronic liver failure or who had previous liver diseases; opinion articles; case reports; articles in languages other than English, Portuguese, or Spanish.

According to the inclusion and exclusion criteria, a primary selection was conducted by reading the title and the abstract. Further research was conducted using secondary terms and reviewing references of the selected articles.

DISCUSSION

Prognostic criteria in ALF

Several prognostic models have been proposed to identify ALF patients with a higher probability of mortality, and will benefit most with LT.[6] The ideal outcome prediction model should be accurate and easy-to-use and accepted by medical staff.[7] The accuracy ensures high sensitivity, thus limiting the number of patients who are not listed for LT and would potentially not survive; and it should also have high specificity, thus limiting the number of patients who would recover spontaneously without LT (i.e., limiting *unnecessary LT*).

King's College criteria (KCC) were the first to be proposed to evaluate poor prognosis in ALF. Due to the rarity of ALF, KCC have been studied in smaller and retrospective cohorts.[8] There are few, but reliable, meta-analysis summarizing the results from these smaller studies about the performance of KCC in ALF (Table 1).[8-11] Overall, KCC demonstrate good prognostic accuracy, particularly in acetaminophen-induced ALF (AALF) when compared with non-acetaminophen-induced ALF (NAALF).[11] In AALF, KCC showed high sensitivity, but limited specificity;[8,9] in NAALF it has moderate sensitivity and higher specificity.[10] So far, KCC remained the main prognostic criteria to select ALF patients for LT, not only because of its clinical simplicity, but also as it can be calculated with clinical criteria and bedside tests.[10]

New marker studies have reported better diagnostic performance than KCC. Some included new markers, others were developed to predict outcomes in other conditions (e.g., model for end-stage liver disease, MELD).

Clichy criteria includes HE grade and factor V levels. Ichai *et al.*[12] found that Clichy criteria had lower specificity than KCC in AALF, and lower sensitivity in NAALF. These criteria are manly used in France and were not widely validated by larger studies.

The MELD score was first used to select patients with chronic liver disease for LT.[13] Two studies showed that MELD had better prognostic accuracy in NAALF than in AALF, because acetaminophen-induced ALI shows higher levels of transaminases and a delayed increase of bilirubin.[11,13] McPahil *et al.*[11] also showed that MELD performed slightly better in NAALF than KCC. Furthermore, Schmidt *et al.*[13] showed that a higher MELD score was linked to the development of HE in patients with severe acetaminophen-induced ALI, although failing to find a correlation between MELD and survival at the time of HE onset. Thus, MELD could be used to predict the development of ALF in the pre-HE phase of acetaminophen-induced ALI. However, MELD cannot be used to select patients to be included on waiting lists for LT, because that decision must be made as soon as patients develop HE. Bechmann *et al.*[14] studied two different epitopes of cytokeratin-18 (CK-18): a) M30, which is exposed after cleavage of CK-18 by caspase-3, and b) M65, which is exposed in all variants of CK-18. The authors found that M65 is a more reliable prognostic marker in ALF, and proposed a modified MELD score (MELD-M65), in which bilirubin is replaced by M-65; they found that MELD-M65 increased prognostic power significantly (Table 1).

Table 1. Sensitivity and specificity of prognostic criteria used in ALF of included studies.

Authors, year of publication and reference	Years included in the study	Criteria	Etiology	Number of patients	Sensitivity (%)	Specificity (%)	AUROC	Comment
Craig *et al.*, 2010[8]	1973–2007	KCC	AALF	1960	58 (53–63)	95 (93–96)	0.91 (0.79–0.99)	–
Bailey *et al.*, 2003[9]	1989–2000	KCC	AALF	880	69 (63–75)	92 (81–97)	0.61 (0.55–0.67)	–
McPhail *et al.*, 2010[10]	1975–2009	KCC	NAALF	1105	68 (59–77)	82 (75–88)	0.855	–
McPhail *et al.*, 2016[11]	2001–2015	KCC	All	2153	59 (56–62)	79 (77–81)	0.76	–
			AALF	–	58 (51–65)	89 (85–93)	–	
			NAALF	–	58 (54–63)	74 (69–78)	–	
		MELD	All	2101	74 (71–77)	67 (64–69)	0.78	
			AALF	–	80 (74–86)	53 (47–59)	–	
			NAALF	–	76 (72–80)	73 (69–78)	–	
Ichai *et al.*, 2015[12]	1997–2010	Clichy	All	173	71	53	–	LT patients excluded
			AALF	–	75	56	–	
			NAALF	–	69	50	–	
Schmidt *et al.*, 2007[13]	1999–2004	MELD	AALF	124	60	69	0.58 (0.47–0.69)	At day 1 of HE
Bechmann *et al.*, 2010[14]	2006–2009	MELD–M65	All	68	81 (64–98)	82 (69–95)	–	At admission
					85 (69–100)	76 (60–91)	–	At M–65 peak value
		MELD			88	30	0.61	–
Rutherford *et al.*, 2012[15]	1998-2011	ALFSG-PI	All	500	86	65	0.822	-
			AALF	-	81	78	-	
			NAALF	-	85	60	-	
Figorilli *et al.*, 2017[16]	1990-2015	ALF-OFs	AALF	-	83	83	0.890	5.58 cut-off value
		KCC			87	40	0.654	-
Agrawal *et al.*, 2021[18]	2017-2019	NK cells	ALF	50	81	83	0.823	-
		Lactate-NK cells			96	79	0.943	
Feng *et al.*, 2014[22]	2010-2012	KCC	All	69	49	83	0.659 (0.528-0.790)	-
		MELD			70	81	0.776 (0.662-0.890)	24.5 cut-off value
		ICGR15			91	61	0.793 (0.688-0.898)	49.8% cut-off value
		ICGR15-MELD Model			88	72	0.855 (0.768-0.942)	-0.4686 cut-off value

AALF: acetaminophen-induced acute liver failure; ALF: acute liver failure; ALFSG-PI: Acute Liver Injury Study Group prognostic index; AOD: acetaminophen overdose; AUROC: area under the receiving operating characteristic; HE: hepatic encephalopathy; ICGR15: indocyanine green retention rate at the 15 minutes; KCC: King's College criteria; LT: liver transplantation; MELD: model for end-stage of liver disease; MELD-M65: model for end-stage of liver disease–M65; NAALF: non-acetaminophen-induced acute liver failure; NK: natural killer.

Prognostic criteria in AALF

AALF is one of the most common aetiologies in Western countries. Therefore, specific prognosis models were developed to improve accuracy.

Rutherford *et al.*[15] developed the Acute Liver Failure Study Group prognostic index (ALFSG-PI), a new model including entry level coma grade, bilirubin, international normalised ratio, phosphorus, and entry level $\log_{10}$M30. ALFSG-PI showed higher acuity in the prediction of mortality and need for LT in AALF than other models, such as MELD and even KCC. The authors state that the inconvenience of an additional enzyme-linked immunosorbent assay (ELISA) to measure M30 levels is counterbalanced by the improvement in accuracy that ALFSG-PI provides.

More recently, Figorilli *et al.*[16] found that the Chronic Liver Failure Consortium organ failure score (CLIF-C OFs) and the dose of norepinephrine required to maintain mean arterial pressure > 70 mmHg were associated with poor prognosis, thus developing a new score: ALF organ failure score (ALF-OFs). Using a cut-off of 5.58, ALF-OFs has higher accuracy than KCC predicting 3-month survival in AALF patients. However, further studies are needed.

Improving prognostic criteria

Several markers, such as serum and image markers, and biomarkers, were proposed to improve the performance of previous prognostic criteria.

Regarding arterial blood lactate, recent evidence showed that one-point time lactate measurement cannot predict survival in AALF, but persistent hyperlactatemia showed better results, thus emphasizing the importance of serial measurements.[17] Recently, Agrawal *et al.*[18] found that natural killer (NK) cell levels were significantly lower in ALF patients, and particularly among those who did not survive. Although pathophysiology is not fully understood, the reduction in NK circulating cells in non-survivors was a result of recruitment of NK cells to liver parenchyma, which could explain liver damage. The authors found that combined lactate and NK cell levels could predict survival with good acuity.

Studies performed in Japan evaluated the potential role of computed tomography (CT) scan in predicting prognosis in ALF. However, caution should be exercised when interpreting those results, because there are major differences in aetiologies between Western countries and Japan. A European study conducted by Zabron *et al.*[19] found that a reduction of liver volume (< 1000 cm^3) was only related to survival in specific aetiologies, such as DILI and indeterminate aetiology of ALF. Interestingly, they found that reduced liver volume in patients with DILI without HE was associated with an increased probability of developing HE at a later stage, suggesting that a CT scan could predict the development of HE.

Scintigraphy with Tc-99m GSA (a synthetic asialoglycoprotein that binds to its receptor exclusively on the surface of hepatocytes) can evaluate liver function in ALF patients.[20] Tatsumi *et al.*[20] found that Tc-99m GSA scintigraphy measurements were significantly associated with 28-day mortality. These results were later supported by Suzuki *et al.*[21] Although it is a relatively expensive exam—and not very feasible as ALF patients require critical care management—, it is minimally invasive and could be an adjuvant prognostic tool.

Indocyanine green (ICG) can also be used as a dynamic liver function test, and its clearance can be assessed using non-invasive techniques. Feng *et al.*[22] developed a new model to predict outcome, including MELD and ICG clearance. This model outperformed KCC (Table 1); however, KCC had a very poor performance, which could be explained by the different aetiologies of ALF in different regions, suggesting that new studies are needed.

Regarding biomarkers, recent advances have been made in the field of microribonucleic acid (miRNA) and extracellular vesicles (particularly microvesicles).

Studies showed that single miRNA parameters should not be used as a prognostic tool, because individual miRNA may regulate multiple genes, and a single gene may be regulated by multiple miRNA. So, miRNA signatures can be used to improve prognostic models or to develop new ones.[23] Salehi *et al.*[24] found changes in serum miRNA profile of AALF patients who had poor prognosis. The dominant miRNA expression changes associated with survival were miRNA-30a, -29b, -140, -26a, -17, and -217. They also found an overlap of miRNA-23a, -150, and -503 expression with a previous study.[25] This miRNA profile is known to drive proliferation, innate immunity, and angiogenesis.[24] Subsequently, Tavabie *et al.*[23] developed a miRNA-based 21-day mortality outcome prediction model. The early time-point model included miRNA-150, -27a, -149, -191, and -20a. The late time-point model included miRNA-122, -30a, -149, -191, and -16-2. In addition to the miRNA panels, the authors incorporated clinical variables (MELD score and vasopressor use) in the final model. This study concluded that miRNA-based early time-point model outperformed MELD score, ALFSG-PI with or without a threshold value and KCC. However, miRNA-based late time-point model only outperformed the KCC and ALFSG-PI with a threshold value, and did not outperform MELD score and ALFSG-PI without a threshold.

Microvesicles are extracellular vesicles with a size ranging from 100–200 nm to 1 μm. So far, most studies compared patients with ALI to healthy controls, thus limiting their clinical relevance[26] excepting one study conducted by Stravitz *et al.*[27] In this study, the authors observed higher microvesicles levels (particularly procoagulant microparticles expressing tissue factor) in patients with systemic inflammatory response syndrome (SIRS), and high-grade HE. They also found that microparticles with a size ranging from 0.28 to 0.64 μm were associated with 21-day outcome of ALI/ALF.

The results on outcome prediction obtained with miRNA and procoagulant microvesicles are promising, but further studies are needed to validate these findings. However, these measurements require advanced non-routinely used equipment, making it difficult to use them as bedside tests to evaluate prognosis in ALF patients.

Futility of LT in ALF

Clinicians have not yet found an ideal prognostic model to select ALF patients for LT. Some models show low sensitivity, while others have low specificity. However, clinicians tend to prefer models with higher sensitivity, that favour the patient, but it increases the occurrence of *unnecessary LT*. Indeed, there are circumstances where performing LT does not alter patient outcome, such as when patients suffer from such severe disease that they will not survive even after LT. So far, there is not an accurate definition for futility in LT.[6] Several factors can influence patient survival: (1) waiting time for graft availability; (2) clinical condition of the patient at the time of LT; (3) quality of the graft; (4) intra- and post-operative care.[28]

Barshes *et al.*[29] created a scoring system to predict survival after LT, using risk factors determined at the time of listing for LT. The final model included four risk factors: (1) history of life support; (2) age > 50 years; (3) BMI ³ 30 kg/m²; (4) creatinine > 2 mg/dL. Patients with all four risk factors had a 5-year survival of 43.5%, and patients without a risk factor had a 5-year survival of 82%.

Bernal *et al.*[28] analysed data from 1,379 ALF patients with grade 3 or 4 HE, and found four factors associated with post-LT mortality: (1) age > 45 years; (2) year of listing; (3) use of vasopressors; (4) high-risk graft (defined as any two of the following: ABO mismatch, steatosis, donor age > 60 years, non-whole graft). The association between survival and recipient age was linked to an age-related reduction in physiologic reserve. A quarter of patients died while waiting for an available graft, confirming that not only is there a narrow *window of opportunity* for LT in critical ill ALF patients, but also that death was more common in patients with AALF, use of vasopressors and blood groups other than A. These data reinforce the importance of aetiology in the clinical outcome. Paradoxically, AALF patients not listed for LT had better survival than other causes of ALF.[28]

Germani *et al.*[3] analysed data from 4,903 adult ALF patients who received LT between 1988 and 2009. The authors found an improvement in survival rate after LT over time, despite the increasing donor age, reflecting a worldwide trend. A graft donor age > 60 years is a well-established adverse factor for LT. However, this was counter-balanced by several factors, such as better anaesthetic and intensive care management, and new immunosuppressor agents. The authors also suggested that LT should be avoided in male patients older than 50 who received grafts from donors > 60 years, ABO mismatching and a reduced size graft.

Figorilli *et al.*[16] found that ALF-OFs (cut-off value of 8.5) could also predict mortality after LT in AALF. This new score had a good performance in predicting futility of LT, with high sensitivity (100%) and acceptable specificity (79.2%). ALF-OFs subdivided AALF patients into different categories: patients who are likely to survive without LT (ALF-OFs > 4.5); patients with high risk of death without LT (ALF-OFs 4.5-8.5); patients with high risk of futile LT (ALF-OFs > 8.5).

Survival after LT in ALF increased in recent years, although it is not comparable with survival in elective LT. According to the studies above, increased age and high-risk graft, including ABO incompatibility, are the main risk factors associated with poor outcome after LT. Lower graft quality can be explained due to organ allocation policies, which prioritize ALF patients.[6] Although the studies of Barshes *et al.*[29] and Bernal *et al.*[28] provide an insight into the risk factors associated with mortality in patients on the waiting list or after LT, they did not provide a practical guidance about decision making regarding the patient. The results of Germani *et al.*[3] are encouraging, but need to be confirmed by further investigation.

Extracorporeal liver support systems

Artificial liver support systems

In ALF, total albumin carrying capacity is decreased as a result of decreased albumin production by hepatocytes and increased hydrophobic toxins load. This principle is known as the toxin and albumin hypothesis.[5] Besides its oncotic pressure effect, albumin can be used as a binding and scavenging molecule to remove toxins from blood,[30] under the assumption that removing these toxins from plasma will improve clinical state and outcome in ALF.[31] This principle was incorporated in albumin-based artificial ECLS, which are based on adsorption and filtration principles, and classified in two groups: dialysis-based techniques (i.e., MARS, SPAD and HDF) and plasma adsorption techniques (i.e., HV-TPE, FPSA and hemadsorption).[30]

Molecular adsorbent recirculating system (MARS) technique mimics a hepatocyte membrane by transferring albumin-binding and water-soluble toxins from patient blood to a dialysate solution through a permeable hollow fibre membrane. Albumin serves as the dialysate solution, which is regenerated by flowing through two adsorbent columns and a second dialyzer, acting as a haemodialysis module.[32] Hollow fibre membrane has a small pore size preventing molecules with a molecular weight > 50 KDa (i.e., essential hormones and growth factors) from crossing the membrane and be removed from patient's blood.[5] Kantola *et al.*[33] performed a controlled single-centre study with 159 ALF patients. Due to the large difference in aetiology between MARS and control groups, overall survival could not be determined directly. In subgroup analysis, the authors found that MARS improved survival in unknown aetiology patients: those who received LT (91% vs. 69%) and patients who did not received LT (20% vs. 8%). Saliba *et al.*[34] performed the unique randomized, controlled, multicentre trial with 102 ALF patients, which found that MARS was not effective in improving 6-month overall survival in ALF compared with standard medical treatment (SMT). The authors also found that post-LT survival was higher than expected, which could be explained by better medical and surgical management, and lower time waiting for LT (16 h). However, in the subgroup analysis, the authors found that MARS improved LT-free survival both in AALF patients and those who received three or more MARS treatment sessions. Gerth *et al.*[35] did not find clear evidence that MARS improved survival in ALI. However, they found that a rapid response to MARS was predictive of a sustained response after its suspension. Recently, Camus *et al.*[36] found that MARS improved survival in AALF and in those patients who received more than three sessions of MARS treatment, reinforcing the results previously found by Saliba *et al.*[34] Although larger randomized and controlled studies with MARS failed to demonstrate clear improvement in survival in ALF patients, Schmidt *et al.*[37] found that

MARS has benefits in hemodynamics, and in clinical and laboratory parameters, thus reinforcing the toxin hypothesis. MARS treatment was generally well-tolerated, although one case of dialysis-induced hypotension was reported.

Unlike MARS, single-pass albumin dialysis (SPAD) uses a single conventional continuous renal replacement therapy machine, without the need for additional columns/filters. Patient blood is dialyzed against an albumin dialysate solution across a permeable high-flux membrane.[5] Karvellas *et al.*[38] found that SPAD is safe, but did not improve clinical and laboratory parameters. Later, Sponholz *et al.*[39] found that both SPAD and MARS significantly decreased bilirubin levels without differences between the two methods. However, reduction in total bile acids and an increase in albumin-binding capacity was only demonstrated during MARS treatment. MARS had also a higher decrease in water-soluble substances, whereas SPAD had higher rates of metabolic disorder complications. Schmuck *et al.*[40] found that dialysate flow rates lower than 700 mL/h were less effective in removing albumin-binding toxins, and bile acids detoxification reached a maximum at a dialysate flow of 1000 mL/h. However, increasing dialysate flow rates not only has technical limitations, but also increases treatment costs.

Hemodiafiltration (HDF) combines diffusion (e.g., hemodialysis) and convection (e.g., hemofiltration) techniques.[41] Fujiwara *et al.*[42] found that both high-volume filtrate and high-flow dialysate continuous HDF techniques had higher rates of restoration of consciousness in ALF patients. However, this study did not find significant differences in survival, and did not include a control group to understand the impact of these therapeutics on overall survival. Takikawa *et al.*[43] showed that continuous HDF improved restoration of consciousness. However, it failed to improve prognostic in patients who had not received LT. The authors found a significant reduction in ammonia and glutamine levels, but also a strong renal replacement effect. However, the effect of HDF on cytokine dynamics remains controversial.

In high-volume therapeutic plasma exchange (HV-TPE), patient plasma is separated from the whole blood using plasmapheresis techniques, and then exchanged for fresh frozen plasma at a ratio of 15% of ideal body weight. This therapeutic is well-established in other immunologically-mediated disorders, and previous case series demonstrated to be a safe procedure and one which improved clinical and laboratory parameters in ALF patients.[44] Larsen *et al.*[44] performed a clinical trial with 182 ALF patients, and found that 3-month survival only improved in patients who had received HV-TPE, but who had not received LT when compared with SMT. Similarly to Saliba *et al.*[34], this finding may be explained by low mean waiting time for an available graft for LT (4.6 days in HV-TPE patients vs. 3.7 days in SMT patients). The authors also found that HV-TPE modulates both pro- and anti-inflammatory responses, thus enabling a longer time for liver regeneration, corroborating the enhancement in survival with HV-TPE treatment. They found a significant reduction in circulating damage associated molecular patterns (DAMPs), immune mediators (e.g., TNF-α, IL-6, IL-8, IL-10) and immune cells expression markers (e.g., CD163, CD64, CCR7 in monocytes; L-selectin in neutrophils), which was accompanied by a decrease in SIRS and sequential organ failure assessment (SOFA) scores. For this reason, they hypothesized that HV-TPE modulates migratory capabilities of circulating innate immune cells, decreasing the liver insult and MOF.[44] Recently Maiwall *et al.*[45] found that standard TPE is associated with improvement of 21-day LT-free survival in NAALF. The authors considered that TPE in higher volumes could worsen cerebral oedema and blood volume. In fact, they observed that standard TPE improved cerebral oedema, and SIRS and SOFA criteria, and significantly decreased ammonia levels, which are known to be associated with cerebral oedema. They also observed a significant reduction in laboratory parameters, DAMPs, endotoxins, and proinflammatory cytokines. However, it also reduced essential growth factors to liver regeneration. Therefore, it is important to balance the benefit of removing toxin mediators and the risk of removing beneficial factors for liver regeneration.

Fractionated plasma separation and adsorption (FPSA, Prometheus) separates patient plasma through an albumin-permeable filter with a molecular weight cut-off of 250 KDa. This fractionated plasma containing patient albumin flows through two adsorbent columns, before returning to circulation. The blood is also treated by high-flux haemodialysis.[30] Until now, there are not any randomized controlled study using FPSA in ALF. Several case series have repeatedly demonstrated that FPSA has a beneficial role in improving clinical and laboratory parameters, and in hemodynamic stability.[46-48] Grodzicki *et al.*[49] estimated that the mortality rates with SMT+FPSA+LT, SMT+FPSA, and SMT alone were 33%, 68%, and > 90%, respectively.

Hemadsorption (CytoSorb) uses an adsorption column to adsorb molecules with a molecular weight < 55 KDa, which was primarily used to treat sepsis.[50] Dhokia *et al.*[50] reported two cases of ALF successfully treated using CytoSorb, thus reducing bilirubin and bile acids levels significantly. Recently, Tomescu *et al.*[51] showed a significant reduction in several laboratory parameters, and in SOFA score after CytoSorb therapy. The main side effect reported was thrombocytopenia, although it was not associated with higher rates of bleeding disorders. The improvement in laboratory parameters using this technique is promising, although more studies are needed.

Bioartificial liver support systems

Bioartificial (or cell-based) ECLS systems incorporate artificial ECLS technology with living hepatocytes in dialysis cartridges that function as a bioreactor, and can incorporate human (ELAD) or porcine hepatocytes (HepatAssist).[5]

Extracorporeal liver assist device (ELAD) is a bioartificial ECLS that incorporates human hepatoblastoma cells in a dialysis cartridge.[52] Ellis *et al.*[52] performed a pilot-controlled study with 24 ALF patients, which failed to prove an increase in survival in patients treated with ELAD. However, this study showed that this technique could function over long periods of time, and showed improvement in some clinical findings. ELAD also influenced spontaneous recovery in approximately 13% of patients who were listed for, but did not received LT.

HepatAssist is a porcine hepatocyte-based bioartificial ECLS.[53] Demetriou *et al.*[53] found no significant differences on 30-day survival between two groups of ALF patients; however, there was a trend toward survival in patients treated with HepatAssist. The authors confirmed that patient subgroup who received LT had significantly higher overall survival, regardless of receiving treatment with HepatAssist. These findings were also influenced by short waiting time for an available graft for LT.

CONCLUSION

A lack of uniformization of selection criteria for LT in ALF patients remains until today. KCC continue to be the most used criteria to select ALF patients for LT in Europe, although previous studies have shown their limited sensitivity. In recent years, several sera and image markers have been proposed to increase accuracy of KCC. However, these studies either involved a reduced number of patients, limiting the reliability of conclusions which can be drawn, or samples which were heterogeneous. This is largely explained by the fact that ALF is a rare and heterogeneous syndrome, varying its presentation significantly according to its aetiology. Recently, several biomarkers have been proposed as potential prognostic markers, as a result of a more detailed study on physiopathology, such as cell death markers. Nevertheless, accurate selection of ALF patients who will not survive without LT remains pivotal. It is, therefore, important to encourage new comprehensive studies (randomized and controlled) evaluating clinical outcomes of the disease and, furthermore, to continue investigating the mechanisms of disease also, to find better prognostic tools. New studies need to be performed to evaluate the impact of the improvement of standard medical therapy and peri- and post-surgical care on mortality in recent years, and how it could affect prognostic models in ALF.

Despite major differences between prognostic criteria, we found that aetiology of ALF and HE grade were the two most important factors that influence spontaneous survival and should therefore be considered when recommending LT. There is a small number of studies on the identification of patients for whom LT is unnecessary. LT is a highly complex and expensive procedure, and is limited to the grafts available, which is why effective management of available organs is vital. Most of ECLS devices improved several clinical and laboratory parameters associated with mechanisms of disease, but there is no clear evidence that overall survival in ALF patients improved.

Artificial liver support systems showed more promising results than bioartificial systems. Particularly, the studies analysed in this review suggest that both MARS and HV-TPE can be used as a *bridge* therapeutic modality to LT in ALF patients. We propose that new studies should be carried out to evaluate these techniques as *bridge* therapies. Moreover, throughout this research we found that more studies and articles have been published about the use of these devices in ACLF than ALF. Therefore, we reiterate the need for more randomized and controlled studies using larger and well-characterized cohorts in ALF.

CONFLICT OF INTEREST

Nothing to declare.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Dias DM, Diogo D, Madaleno J and Tralhão JG; **Conception and design**: Dias DM, Diogo D, Madaleno J and Tralhão JG; **Data analysis and interpretation**: Dias DM, Diogo D, Madaleno J and Tralhão JG; **Article writing**: Dias DM; **Critical revision**: Dias DM, Diogo D, Madaleno J and Tralhão JG; **Final approval**: Diogo D, Madaleno J and Tralhão JG.

AVAILABILITY OF RESEARCH DATA

All data sets were generated or analyzed in the current study.

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REFERENCES

1. European Association for the Study of the Liver. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66(5):1047-81. https://doi.org/10.1016/j.jhep.2016.12.003
2. Stravitz RT, Lee WM. Acute liver failure. Lancet. 2019;394(10201):869-81. https://doi.org/10.1016/s0140-6736(19)31894-x
3. Germani G, Theocharidou E, Adam R, Karam V, Wendon J, O'Grady J, et al. Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. J Hepatol. 2012;57(2):288-96. https://doi.org/10.1016/j.jhep.2012.03.017
4. Struecker B, Raschzok N, Sauer IM. Liver support strategies: cutting-edge technologies. Nat Rev Gastroenterol Hepatol. 2014;11(3):166-76. https://doi.org/10.1038/nrgastro.2013.204
5. MacDonald AJ, Karvellas CJ. Emerging role of extracorporeal support in acute and acute-on-chronic liver failure: Recent developments. Semin Respir Crit Care Med. 2018;39(5):625-34. https://doi.org/10.1055/s-0038-1675334
6. O'Grady J. Timing and benefit of liver transplantation in acute liver failure. J Hepatol. 2014;60(3):663-70. https://doi.org/10.1016/j.jhep.2013.10.024
7. Craig DG, Reid TW, Martin KG, Davidson JS, Hayes PC, Simpson KJ. The systemic inflammatory response syndrome and sequential organ failure assessment scores are effective triage markers following paracetamol (acetaminophen) overdose. Aliment Pharmacol Ther. 2011;34(2):219-28. https://doi.org/10.1111/j.1365-2036.2011.04687.x
8. Craig DG, Ford AC, Hayes PC, Simpson KJ. Systematic review: prognostic tests of paracetamol-induced acute liver failure. Aliment Pharmacol Ther. 2010;31(10):1064-76. https://doi.org/10.1111/j.1365-2036.2010.04279.x
9. Bailey B, Amre DK, Gaudreault P. Fulminant hepatic failure secondary to acetaminophen poisoning: A systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation. Crit Care Med. 2003;31(1):299-305. https://doi.org/10.1097/00003246-200301000-00048
10. McPhail MJ, Wendon JA, Bernal W. Meta-analysis of performance of Kings's College Hospital criteria in prediction of outcome in non-paracetamol-induced acute liver failure. J Hepatol. 2010;53(3):492-9. https://doi.org/10.1016/j.jhep.2010.03.023
11. McPhail MJ, Farne H, Senvar N, Wendon JA, Bernal W. Ability of King's College criteria and model for end-stage liver disease scores to predict mortality of patients with acute liver failure: A meta-analysis. Clin Gastroenterol Hepatol. 2016;14(4):516-25.e5; quiz e43-5. https://doi.org/10.1016/j.cgh.2015.10.007
12. Ichai P, Legeai C, Francoz C, Boudjema K, Boillot O, Ducerf C, et al. Patients with acute liver failure listed for superurgent liver transplantation in France: Reevaluation of the Clichy–Villejuif criteria. Liver Transpl. 2015;21(4):512-23. https://doi.org/10.1002/lt.24092
13. Schmidt LE, Larsen FS. MELD score as a predictor of liver failure and death in patients with acetaminophen-induced liver injury. Hepatology. 2007;45(3):789-96. https://doi.org/10.1002/hep.21503
14. Bechmann LP, Jochum C, Kocabayoglu P, Sowa JP, Kassalik M, Gieseler RK, et al. Cytokeratin 18-based modification of the MELD score improves prediction of spontaneous survival after acute liver injury. J Hepatol. 2010;53(4):639-47. https://doi.org/10.1016/j.jhep.2010.04.029
15. Rutherford A, King LY, Hynan LS, Vedvyas C, Lin W, Lee WM, et al. Development of an accurate index for predicting outcomes of patients with acute liver failure. Gastroenterology. 2012;143(5):1237-43. https://doi.org/10.1053/j.gastro.2012.07.113
16. Figorilli F, Putignano A, Roux O, Houssel-Debry P, Francoz C, Paugam-Burtz C, et al. Development of an organ failure score in acute liver failure for transplant selection and identification of patients at high risk of futility. PLoS One. 2017;12(12):e0188151. https://doi.org/10.1371/journal.pone.0188151
17. Bernal W. Lactate is important in determining prognosis in acute liver failure. J Hepatol. 2010;53(1):209-10. https://doi.org/10.1371/journal.pone.0188151
18. Agrawal T, Maiwall R, Rajan V, Bajpai M, Jagdish RK, Sarin SK, et al. Higher circulating natural killer cells and lower lactate levels at admission predict spontaneous survival in non-acetaminophen induced acute liver failure. Clin Immunol. 2021;231:108829. https://doi.org/10.1016/j.clim.2021.108829
19. Zabron A, Quaglia A, Fatourou E, Peddu P, Lewis D, Heneghan M, et al. Clinical and prognostic associations of liver volume determined by computed tomography in acute liver failure. Liver Int. 2018;38(9):1592-601. https://doi.org/10.1111/liv.13725
20. Tatsumi H, Masuda Y, Imaizumi H, Yoshida S, Goto K, Yama N, et al. Asialoglycoprotein receptor scintigraphy with 99mTc-galactosyl human serum albumin (99mTc-GSA) as an early predictor of survival in acute liver failure. Anaesth Intensive Care. 2013;41(4):523-8. https://doi.org/10.1177/0310057x1304100414

21. Suzuki Y, Kakisaka K, Sato T, Mikami R, Abe H, Sasaki T, et al. Tc-99m GSA scintigraphy within the first 3 days after admission as an early predictor of outcome in severe acute liver injury. Sci Rep. 2021;11(1):12518. https://doi.org/10.1038/s41598-021-92058-6

22. Feng HL, Li Q, Wang L, Yuan GY, Cao WK. Indocyanine green clearance test combined with MELD score in predicting the short-term prognosis of patients with acute liver failure. Hepatobiliary Pancreat Dis Int. 2014;13(3):271-5. https://doi.org/10.1016/s1499-3872(14)60040-0

23. Tavabie OD, Karvellas CJ, Salehi S, Speiser JL, Rose CF, Menon K, et al. A novel microRNA-based prognostic model outperforms standard prognostic models in patients with acetaminophen-induced acute liver failure. J Hepatol. 2021;75(2):424-34. https://doi.org/10.1016/j.jhep.2021.03.013

24. Salehi S, Tavabie OD, Verma S, McPhail MJW, Farzaneh F, Bernal W, et al. Serum MicroRNA signatures in recovery from acute and chronic liver injury and selection for liver transplantation. Liver Transpl. 2020;26(6):811-22. https://doi.org/10.1002/lt.25781

25. Salehi S, Brereton HC, Arno MJ, Darling D, Quaglia A, O'Grady J, et al. Human liver regeneration is characterized by the coordinated expression of distinct microRNA governing cell cycle fate. Am J Transplant. 2013;13(5):1282-95. https://doi.org/10.1111/ajt.12183

26. Thietart S, Rautou PE. Extracellular vesicles as biomarkers in liver diseases: A clinician's point of view. J Hepatol. 2020;73(6):1507-25. https://doi.org/10.1016/j.jhep.2020.07.014

27. Stravitz RT, Bowling R, Bradford RL, Key NS, Glover S, Thacker LR, et al. Role of procoagulant microparticles in mediating complications and outcome of acute liver injury/acute liver failure. Hepatology. 2013;58(1):304-13. https://doi.org/10.1002/hep.26307

28. Bernal W, Cross TJ, Auzinger G, Sizer E, Heneghan MA, Bowles M, et al. Outcome after wait-listing for emergency liver transplantation in acute liver failure: a single centre experience. J Hepatol. 2009;50(2):306-13. https://doi.org/10.1016/j.jhep.2008.09.012

29. Barshes NR, Lee TC, Balkrishnan R, Karpen SJ, Carter BA, Goss JA. Risk stratification of adult patients undergoing orthotopic liver transplantation for fulminant hepatic failure. Transplantation. 2006;81(2):195-201. https://doi.org/10.1097/01.tp.0000188149.90975.63

30. Karvellas CJ, Subramanian RM. Current evidence for extracorporeal liver support systems in acute liver failure and acute-on-chronic liver failure. Crit Care Clin. 2016;32(3):439-51. https://doi.org/10.1016/j.ccc.2016.03.003

31. Larsen FS. Artificial liver support in acute and acute-on-chronic liver failure. Curr Opin Crit Care. 2019;25(2):187-91. https://doi.org/10.1097/mcc.0000000000000584

32. Stange J, Mitzner SR, Risler T, Erley CM, Lauchart W, Goehl H, et al. Molecular adsorbent recycling system (MARS): clinical results of a new membrane-based blood purification system for bioartificial liver support. Artif Organs. 1999;23(4):319-30. https://doi.org/10.1046/j.1525-1594.1999.06122.x

33. Kantola T, Koivusalo AM, Höckerstedt K, Isoniemi H. The effect of molecular adsorbent recirculating system treatment on survival, native liver recovery, and need for liver transplantation in acute liver failure patients. Transpl Int. 2008;21(9):857-66. https://doi.org/10.1111/j.1432-2277.2008.00698.x

34. Saliba F, Camus C, Durand F, Mathurin P, Letierce A, Delafosse B, et al. Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: A randomized, controlled trial. Ann Intern Med. 2013;159(8):522-31. https://doi.org/10.7326/0003-4819-159-8-201310150-00005

35. Gerth HU, Pohlen M, Thölking G, Pavenstädt H, Brand M, Wilms C, et al. Molecular adsorbent recirculating system (MARS) in acute liver injury and graft dysfunction: Results from a case-control study. PLoS One. 2017;12(4):e0175529. https://doi.org/10.1371/journal.pone.0175529

36. Camus C, Locher C, Saliba F, Goubaux B, Bonadona A, Lavayssiere L, et al. Outcome of patients treated with molecular adsorbent recirculating system albumin dialysis: A national multicenter study. JGH Open. 2020;4(4):757-63. https://doi.org/10.1002/jgh3.12359

37. Schmidt LE, Wang LP, Hansen BA, Larsen FS. Systemic hemodynamic effects of treatment with the molecular adsorbents recirculating system in patients with hyperacute liver failure: a prospective controlled trial. Liver Transpl. 2003;9(3):290-7. https://doi.org/10.1053/jlts.2003.50051

38. Karvellas CJ, Bagshaw SM, McDermid RC, Stollery DE, Bain VG, Gibney RT. A case-control study of single-pass albumin dialysis for acetaminophen-induced acute liver failure. Blood Purif. 2009;28(3):151-8. https://doi.org/10.1053/jlts.2003.50051

39. Sponholz C, Matthes K, Rupp D, Backaus W, Klammt S, Karailieva D, et al. Molecular adsorbent recirculating system and single-pass albumin dialysis in liver failure--A prospective, randomised crossover study. Crit Care. 2016;20:2. https://doi.org/10.1186/s13054-015-1159-3

40. Schmuck RB, Nawrot GH, Fikatas P, Reutzel-Selke A, Pratschke J, Sauer IM. Single pass albumin dialysis-a dose-finding study to define optimal albumin concentration and dialysate flow. Artif Organs. 2017;41(2):153-61. https://doi.org/10.1111/aor.12736

41. Tattersall JE, Ward RA. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013;28(3):542-50. https://doi.org/10.1093/ndt/gfs530

42. Fujiwara K, Abe R, Yasui S, Yokosuka O, Kato N, Oda S. High recovery rate of consciousness by high-volume filtrate hemodiafiltration for fulminant hepatitis. Hepatol Res. 2019;49(2):224-31. https://doi.org/10.1111/hepr.13255

43. Takikawa Y, Kakisaka K, Suzuki Y, Ido A, Shimamura T, Nishida O, et al. Multicenter study on the consciousness-regaining effect of a newly developed artificial liver support system in acute liver failure: An on-line continuous hemodiafiltration system. Hepatol Res. 2021;51(2):216-26. https://doi.org/10.1111/hepr.13557

44. Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial. J Hepatol. 2016;64(1):69-78. https://doi.org/10.1016/j.jhep.2015.08.018

45. Maiwall R, Bajpai M, Singh A, Agarwal T, Kumar G, Bharadwaj A, et al. Standard-volume plasma exchange improves outcomes in patients with acute liver failure: A randomized controlled trial. Clin Gastroenterol Hepatol. 2022;20(4):e831-54. https://doi.org/10.1016/j.cgh.2021.01.036

46. Komardina E, Yaroustovsky M, Abramyan M, Plyushch M. Prometheus therapy for the treatment of acute liver failure in patients after cardiac surgery. Kardiochir Torakochirurgia Pol. 2017;14(4):230-5. https://doi.org/10.5114/kitp.2017.72226

47. Sentürk E, Esen F, Ozcan PE, Rifai K, Pinarbaşi B, Cakar N, et al. The treatment of acute liver failure with fractionated plasma separation and adsorption system: Experience in 85 applications. J Clin Apher. 2010;25(4):195-201. https://doi.org/10.1002/jca.20238

48. Skwarek A, Grodzicki M, Nyckowski P, Kotulski M, Zieniewicz K, Michalowicz B, et al. The use Prometheus FPSA system in the treatment of acute liver failure: preliminary results. Transplant Proc. 2006;38(1):209-11. https://doi.org/10.1016/j.transproceed.2005.12.011

49. Grodzicki M, Kotulski M, Leonowicz D, Zieniewicz K, Krawczyk M. Results of treatment of acute liver failure patients with use of the prometheus FPSA system. Transplant Proc. 2009;41(8):3079-81. https://doi.org/10.1016/j.transproceed.2009.08.024

50. Dhokia VD, Madhavan D, Austin A, Morris CG. Novel use of Cytosorb™ haemadsorption to provide biochemical control in liver impairment. J Intensive Care Soc. 202019. p. 174-81. https://doi.org/10.1177/1751143718772789

51. Tomescu D, Popescu M, David C, Sima R, Dima S. Haemoadsorption by CytoSorb® in patients with acute liver failure: A case series. Int J Artif Organs. 2021;44(8):560-4. https://doi.org/10.1177/0391398820981383

52. Ellis AJ, Hughes RD, Wendon JA, Dunne J, Langley PG, Kelly JH, et al. Pilot-controlled trial of the extracorporeal liver assist device in acute liver failure. Hepatology. 1996;24(6):1446-51. https://doi.org/10.1002/hep.510240625

53. Demetriou AA, Brown RS, Jr., Busuttil RW, Fair J, McGuire BM, Rosenthal P, et al. Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. Ann Surg. 2004;239(5):660-7; discussion 667-70. https://doi.org/10.1097/01.sla.0000124298.74199.e5