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Selection Criteria for Liver Transplantation and "Bridge" Therapeutic Modalities in Acute Liver Failure – A Review

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TITLE: SELECTION CRITERIA FOR LIVER TRANSPLANTATION AND "BRIDGE" THERAPEUTIC MODALITIES IN ACUTE LIVER FAILURE – A REVIEW

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LIST OF ABBREVIATIONS

AALF – acetaminophen-induced acute liver failure;
ACLF – acute-on-chronic liver failure;
AF-Gc – actin-free group-specific component;
ALI – acute liver injury;
ALF – acute liver failure;
ALF-OFs – acute liver failure organ failure score;
ALFSG – Acute Liver Injury Study Group;
ALFSG-PI – Acute Liver Injury Study Group prognostic index;
AOD – acetaminophen overdose;
AS-AIH – acute severe autoimmune hepatitis;
AUROC – area under the receiving operating characteristic;
BiLE – bilirubin-lactate-aetiology score;
CK-18 – cytokeratin-18;
CLIF-C OFs – Chronic Liver Failure Consortium organ failure score;
CT – computed tomography;
DAMPs – damage associated molecular patterns;
DILI – drug-induced liver injury;
DNA – deoxyribonucleic acid;
EASL – European Association for the Study of the Liver;
ECLS – extracorporeal liver support systems;
e.g. – *exempli gratia* (for example)
ELAD – extracorporeal liver assist device;
ELTR – European Liver Transplant Registry;
ELV – estimated liver volume;
FPSA – fractionated plasma separation and adsorption;
Gc – group-specific component;
HBV – hepatitis B virus;
HDF – hemodiafiltration;
HE – hepatic encephalopathy;
HV-TPE – high-volume therapeutic plasma exchange;
i.e. – *id est* (that is);
ICG – indocyanine green;
ICGR15 - indocyanine green retention rate at the 15 minutes;
INR – international normalised ratio;
KCC – King's College criteria;
LT – liver transplantation;
MARS – molecular adsorbent recirculating system;

MELD – model for end-stage liver disease;

MeSH – medical subject headings;

miRNA – micro ribonucleic acid;

MOF – multiple organ failure;

NAALF – non-acetaminophen-induced acute liver failure;

NK – natural killer;

RNA – ribonucleic acid;

RRT – renal replacement therapies;

SIRS – systemic inflammatory response syndrome;

SLV – standard liver volume;

SMT – standard medical treatment;

SOFA – sequential organ failure assessment;

SPAD – single-pass albumin dialysis;

Tc-99m GSA – technetium-99m-diethylenetriaminepentaacetic acid galactosyl human serum albumin;

TIPS – transjugular intrahepatic portosystemic shunt;

TPE – therapeutic plasma exchange.

1. ABSTRACT

Introduction: Acute liver failure is a rare syndrome with an incidence of less than 10 cases per million in Europe. The introduction of liver transplantation changed the natural course of the disease, increasing survival rates. However, mortality remains remarkably high. The shortage of organs for transplantation demands a rigorous selection process to determine whom should receive transplantation. In the last decades, several prognostic models have been proposed in order to identify the patients who would benefit the most from liver transplantation. Acute liver failure can progress rapidly to multiple organ failure. Therefore, different extracorporeal liver support systems have been developed to function as a "bridge" to transplantation or spontaneous survival, such as *Molecular Adsorbent Recirculating System* (MARS), Prometheus® or therapeutic plasma exchange.

Objectives: A review of the main selection criteria used for liver transplantation in acute liver failure is carried out, focusing mostly on the new proposed prognostic markers. The purpose of this study is to identify poor prognosis criteria associated with futility in liver transplantation. The main extracorporeal liver support systems are also reviewed, including an analysis of their impact on the survival of patients with acute liver failure.

Methods: MEDLINE and Pubmed databases were searched between 16th October 2021 and 5th December 2021. The inclusion criteria were: adult patients; patients presenting with acute liver injury or acute liver failure; observational studies; clinical studies; case series; case-control studies; systematic reviews; meta-analysis. The exclusion criteria were: 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.

Discussion: King's College criteria have been widely used. Despite good specificity, these criteria have low sensitivity. Several markers have been used to improve prognostic accuracy, but the results are not sufficiently clear. Various studies found that patient age, ABO incompatibility, and poor-quality grafting were potential factors that could indicate potential futility in liver transplantation. Studies including extracorporeal liver support systems revealed that these techniques have a positive influence in clinical and laboratory parameters; however, there is no clear evidence of improvement in survival.

Conclusion: This study concludes that acute liver failure is a very heterogeneous syndrome, which brings into question of the studies carried out to evaluate prognostic criteria to select patients with acute liver failure for liver transplantation. It also narrows down the studies performed to evaluate the impact of extracorporeal liver support systems on survival.

Keywords: acute liver failure; liver transplantation; prognosis; therapeutic futility; extracorporeal liver support.

2. RESUMO

Introdução: A falência hepática aguda é uma síndrome rara, com uma incidência inferior a 10 casos por milhão de pessoas na Europa, mas que mantém uma mortalidade considerável. A introdução da transplantação hepática alterou a história natural desta doença. Contudo, devido à escassez de órgãos disponíveis para transplantação, é necessário selecionar criteriosamente os doentes a transplantar. Por isso, nas últimas décadas têm vindo a ser desenvolvidos vários modelos de prognóstico, de modo a avaliar os doentes que mais podem beneficiar com a transplantação hepática. A falência hepática aguda pode evoluir muito rapidamente para falência multiorgânica. Assim, nos últimos anos têm vindo a ser aperfeiçoados vários sistemas de suporte hepático extracorporal, sendo um dos seus objetivos fazer a "ponte" para a transplantação ou assegurar a recuperação do doente, como o *Molecular Adsorbent Recirculating System* (MARS), o Prometheus® ou a troca plasmática.

Objetivos: Com a realização deste estudo, temos como objetivo fazer uma revisão dos principais critérios de seleção usados para transplantação hepática nos doentes com falência hepática aguda, incidindo sobretudo sobre os novos marcadores que têm sido propostos. Pretendemos também identificar os critérios de mau prognóstico associados a futilidade na transplantação hepática. Temos também como objetivo fazer uma revisão dos principais sistemas de suporte hepático extracorporal, visando analisar 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 que apresentassem lesão hepática aguda ou falência hepática aguda; estudos observacionais; estudos clínicos; séries de casos clínicos; estudos caso-controlo; revisões sistemáticas; meta-análises. Os critérios de exclusão foram: doentes pediátricos; doentes com falência hepática crónica agudizada ou com patologia hepática prévia; artigos de opinião; casos clínicos; artigos em outras línguas que não português, inglês ou espanhol.

Discussão: Os critérios de King's College têm sido amplamente utilizados. No entanto, apesar de terem uma boa especificidade, apresentam uma sensibilidade reduzida. Vários marcadores foram utilizados para melhorar a sua acuidade prognóstica, mas sem resultados claros alcançados até ao momento. Vários estudos têm apontado a idade do doente, a incompatibilidade ABO e má qualidade do enxerto como potenciais fatores que indiquem potencial futilidade na transplantação hepática. Para além disso, estudos feitos sobre os sistemas de suporte hepático extracorporal têm revelado que estes têm uma influência positiva nos parâmetros clínicos e laboratoriais. No entanto, não têm demonstrado um aumento claro da sobrevida destes doentes.

Conclusão: Com este estudo concluímos que a falência hepática aguda é uma síndrome muito 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 na sobrevida dos sistemas de suporte hepático extracorporal.

Palavras-chave: falência hepática aguda; transplantação hepática; prognóstico; futilidade terapêutica; suporte hepático extracorporal.

3. INTRODUCTION

Fulminant hepatic failure was first defined in 1970 by Trey and Davidson as a "potentially reversible condition, the consequence of severe liver injury, with an onset of encephalopathy within 8 weeks of appearance of the first symptoms and in the absence of pre-existing liver disease".[1] It was redefined in 1993 by O'Grady *et al.*[2], who suggested replacing the previous designation with acute liver failure (ALF), and proposed a new classification of this syndrome based on the time between the onset of jaundice and the onset of hepatic encephalopathy (HE) was proposed: hyperacute (within 7 days); acute (between 8 and 28 days); subacute (after 28 days). If HE starts 24 weeks after the onset of jaundice, chronic liver failure should be considered.[2] This new classification helps distinguishing different causes, clinical patterns, and prognosis of ALF. Hyperacute ALF is mainly caused by acetaminophen toxicity and ischaemia. It is associated with very high levels of aminotransferases, and lower bilirubin concentrations,[3] whereas slow evolving liver injuries (acute and subacute forms of ALF) are often caused by hepatitis B virus (HBV) infection, autoimmunity, or drug-induced liver injury (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.[3]

ALF is a rare syndrome with an annual incidence of less than 10 cases per million in developed countries.[4] It causes impairment of liver function, culminating in coagulopathy, and HE in the absence of chronic liver disease. Patients with ALF present with increased levels of aminotransferases, jaundice, prolonged international normalised ratio (INR) of prothrombin, and an altered level of consciousness.[3] ALF can affect almost all organ systems, and is often associated with multiple organ dysfunction, such as cardiovascular instability, susceptibility to infection, acute kidney injury, and cerebral oedema, and it may evolve to multiple organ failure (MOF). The presence of HE is an important clinical feature in defining ALF. Once a patient has altered coagulation parameters without altered level of consciousness, it is defined as acute liver injury (ALI), and patients with ALI can develop ALF.[3]

In developed countries, the five most common aetiologies of ALF are acetaminophen toxicity, ischaemia, DILI, 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 hepatic disease: Wilson's disease, reactivation of chronic HBV infection, and autoimmunity.[3]

Liver transplantation (LT) is the only therapeutic available which effectively increases overall survival. Before the era of LT, overall mortality of ALF was about 80-85%. In 2012, Germani *et al.*[5] analysed data from the European Liver Transplant Registry (ELTR) database which were collected over 43 years of LT in Europe. They found that mortality had decreased significantly. In this study, 1, 5 and 10-year survival rates were 74%, 68%, and 63%, respectively. Early post-LT mortality in patients with ALF 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.[5] 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 transplantation, and the risks of immunosuppression. Since ALF can rapidly progress to MOF, it is crucial to assess prognosis of patients as quickly as possible, differentiating those who will recover spontaneously from those who will not survive without LT.[6] 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 (EASL) presented new guidelines on the management of ALF, addressing the lack of uniformity in the criteria used to assess prognosis.[6]

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.[7] In ALF, hepatocellular dysfunction leads to the loss of endogenous hepatic detoxification, as well as metabolic and regulatory functions. This culminates in the accumulation of serum toxins, such as ammonia, proinflammatory cytokines, endogenous benzodiazepines, and aromatic amino acids, which contribute to the development of HE and MOF. Water-soluble metabolites can be removed from the blood using renal replacement therapies (RRT); however, hydrophobic and albumin-binding metabolites cannot be removed using these techniques.[8] Extracorporeal liver support systems (ECLS) are extracorporeal devices that mimic the three primary hepatic functions: (1) detoxification of damaging toxins; (2) biosynthesis, mimicking the synthetic function of hepatocytes (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).[8]

In this study, a review of the most important criteria used to select patients with ALF for LT is proposed, as well as their strengths and weaknesses, and how the accuracy of these prognostic models can be improved, thus addressing the lack of uniformity mentioned above. 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 patients with ALF.

4. METHODS

The MEDLINE and Pubmed databases (https://pubmed.ncbi.nlm.nih.gov) 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 other terms to refine the results, such as *King's College* OR *Kings College* OR *Clichy* OR *APACHE* OR *SOFA* OR *Sequential Organ Failure Assessment* OR *Lactate* OR *Phosphate* OR *Biomarkers* [MeSH] OR *MicroRNA*s [MeSH] OR *Acetaminophen* OR Paracetamol OR *Wilson Disease* OR *Amanita* OR *Amanita Phalloides* OR *Autoimmune Hepatitis*. 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 presenting with acute liver injury or acute liver failure; 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.

5. DISCUSSION

ALF is a rare syndrome with high mortality rates, between approximately 80 and 85% before the era of LT. With the widespread availability of LT, around 25% of patients with ALF received LT, contributing to 10-year survival rates reaching almost 63%, representing now 8% of the total LT in Europe.[5] Despite the assumption that LT was the only available therapy which improves survival by several single centre case series, its effectiveness was not clearly demonstrated and validated in randomized controlled trials. Several prognostic models have been proposed to identify patients with ALF who have a higher probability of mortality, and will benefit most and survive after LT.[9] Thereafter, a summary of the most widely used selection models to predict mortality in ALF will be presented, as well as the newer markers proposed. The ideal outcome prediction model should be accurate and easy-to-use and accept by medical staff.[10] 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").

5.1. Prognostic Criteria in Acute Liver Failure

King's College Criteria

King's College criteria (KCC) (Figure 1) were the first to be proposed to evaluate poor prognosis outcomes in patients with ALF.[11] Due to the rarity of ALF, KCC have been studied in smaller and retrospective cohorts.[12] There are few, but reliable, meta-analysis summarizing the results from these smaller studies about the performance of KCC in ALF.[12-15] Overall, KCC demonstrate good prognostic

accuracy, particularly in acetaminophen-induced acute liver failure (AALF) when compared with non-acetaminophen-induced acute liver failure (NAALF). [15] In AALF, KCC showed high sensitivity, but limited specificity[12, 13]; in NAALF it has moderate sensitivity and higher specificity.[14] So far, KCC remained the main prognostic criteria to select patients with ALF for LT, not only because of its clinical simplicity, but also as it can be calculated with clinical criteria and bedside tests.[14] McPhail *et al.*[14] found an "era effect" in studies published after 1995, showing lower performance compared with previous studies. This could be explained by publication bias or changes in management of critical ill patients. The authors also concluded that KCC are more efficient in patients with high grade HE.[14]

New marker studies have reported better diagnostic performance than KCC. Some included new markers (Clichy criteria), others were developed to predict outcomes in other conditions (e.g., MELD and SOFA). Most of these studies were small in size, with limited methodological quality and are seldom internally or externally validated, and to date, few have been adopted internationally.

FIGURE 1. King's College criteria[11]

Acetaminophen-Induced ALF
pH < 7.30 (irrespective of HE grade)
OR
PT > 100 s and creatinine > 300 μmol/L in patients with grade III or IV HE
Non-Acetaminophen-Induced ALF
PT > 100 s (irrespective of HE grade)
OR
Any 3 of the following variables (irrespective of HE grade):
• age < 10 or > 40 years
• aetiology (non-A and non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions)
• duration of jaundice before the onset of HE > 7 days
• PT > 50 s
• bilirubin > 300 μmol/L

ALF: acute liver failure; HE: hepatic encephalopathy; PT: prothrombin time.

Clichy Criteria

Clichy criteria (Figure 2) were first applied by Bismuth *et al.*[16] for selecting patients with ALF for LT at the hepatology unit of Paul Brousse Hospital in Paris. Izumi *et al.*[17] confirmed that factor V < 20% was associated to lower survival rates; however, a lower cut-off value for factor V levels (< 10%) had a better prognostic value. In a study with 172 patients, Ichai *et al.*[18] found that Clichy criteria had lower specificity than KCC in AALF, and lower sensitivity in NAALF. The authors also suggested that the accuracy of Clichy criteria could be improved by including bilirubin levels and creatinine clearance

in AALF, and bilirubin levels in NAALF. Clichy criteria is not routinely used in most European centres, but remains widely used in France, despite not being widely validated by larger studies.[18]

FIGURE 2. Clichy criteria[16]

Grade III or IV of HE

AND

Factor V levels:

- < 20% of normal value (if patient's age < 30 years)

  OR

- < 30% of normal value (if patient's age ≥ 30 years)

HE: hepatic encephalopathy.

Model for End-stage Liver Disease Score

Model for end-stage liver disease (MELD) score was first used to evaluate short-term prognosis in patients with hepatic cirrhosis undergoing transjugular intrahepatic portosystemic shunt (TIPS) for relieving portal hypertension. It then started being used to predict survival in end-stage chronic liver disease, as well as a severity index in selection of patients with chronic liver disease for LT.[19]

$$\text{MELD} = 9.57 \times \ln(\text{Creatinine[mg/dL]}) + 3.78 \times \ln(\text{Total Bilirubin[mg/dL]}) + 11.20 \times \ln(\text{INR[mg/dL]}) + 6.43$$

In an observational study, Kremers *et al.*[20] found for the first time an association between survival and MELD in patients with ALF awaiting LT. This association was particularly significant in patients diagnosed with NAALF.[20] Indeed, later studies showed that MELD had better prognostic accuracy in NAALF than in AALF, because of the natural history of AALF, in which ALI by acetaminophen shows higher levels of transaminases and a delayed increase of bilirubin.[15, 19]

McPahil *et al.*[15] also showed that MELD performed slightly better in NAALF than KCC. In a prospective study, Schmidt *et al.*[19] showed that a higher MELD score was linked to the development of HE in patients with severe acetaminophen-induced hepatotoxicity, 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-encephalopathic phase of acetaminophen-induced ALI. However, MELD cannot be used to select patients to be included on waiting lists for hepatic transplantation, because that decision has to be made as soon as patients develop HE.[19]

Bechmann *et al.*[21] studied how cell death-associated markers could improve acuity of MELD score. They 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.[21]

$$\text{MELD-M65} = 9.57 \times \ln(\text{Creatinine[mg/dL]}) + 3.78 \times \ln(\text{M65[U/}\mu\text{L]}) + 11.20 \times \ln(\text{INR[mg/dL]}) + 6.43$$

Sequential Organ Failure Assessment

Sequential organ failure assessment (SOFA) is an MOF assessment score which evaluates six system of organs – hepatic, renal, coagulation, cardiovascular, respiratory, and neurological.[10] Craig *et al.* studied the prognostic accuracy of SOFA in acetaminophen overdose (AOD), both single time point AOD[10, 22] and staggered AOD[23]. The results were similar between the three studies, showing that SOFA score had a better performance than MELD and despite its higher specificity, had lower sensitivity when compared with KCC.[10, 22, 23] This results were later supported by other studies in ALF, which suggested SOFA should not be used to select patients with ALF for LT.[24, 25]

5.2. Prognostic Criteria in Specific Acute Liver Failure Aetiologies

Acetaminophen-Induced Acute Liver Failure

Bernal *et al.*[26] developed a new dynamic outcome prediction model for AALF. The final model included clinical and laboratory parameters measured on days 1 and 2 after admission, providing a continuous survival prediction outcome rather than a binary survival outcome. Despite its good performance, this model was not compared with previous models.[26] A subsequent study performed by Koch *et al.*[27] concluded that the dynamic changes on clinical and laboratory variables over time had no statistically significant benefit of predicting outcome in patients with AALF. Although these variables are important in the pathophysiology of ALF, they do not improve model's performance mathematically.[27]

Rutherford *et al.*[28] developed the Acute Liver Failure Study Group prognostic index (ALFSG-PI), a new model combining cell death-associated markers with clinical parameters to predict the need for LT in patients with AALF. The final model includes entry level coma grade, bilirubin, INR, phosphorus, and entry level $\log_{10}$M30. ALFSG-PI showed higher acuity in the prediction of mortality and need for LT in ALF than other prediction 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 over KCC and MELD.[28]

Once apoptosis and necrosis markers were not routinely used, Koch *et al.*[27] developed a new outcome prognostic model – Acute Liver Failure Study Group (ALFSG) model. After performing a regression analysis, the variables which remained statistically significant were HE grade, ALF aetiology severity, vasopressor use, bilirubin, and INR. This study differentiated between the aetiologies of ALF in those with poor spontaneous survival, usually < 30% (acetaminophen toxicity, pregnancy, ischaemia, hepatitis A), and those with better spontaneous survival, usually > 50% (all other causes).[27]

More recently, Frigorilli *et al.*[29] performed a multivariable analysis to identify new criteria that could predict mortality in AALF, testing scores used in acute-on-chronic liver failure (ACLF). The authors found that 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 – acute liver failure organ failure score (ALF-OFs).[29]

$$\text{ALF-OFs} = (0.391 \times \text{CLIF-C OFs}) + (0.020 \times \text{Norepinephrine [µg/min]})$$

CLIF-C OFs ranges from 0 to 18, and it evaluates prognostic in patients with ACLF attending to parameters which reflect six organ systems (liver, kidney, brain, coagulation, circulation, and respiratory system). Using a cut-off of 5.58, ALF-OFs proved to have higher accuracy than KCC predicting 3-month survival in patients with AALF. However, these encouraging results need to be confirmed by studies with larger samples of patients.[29]

Autoimmune Hepatitis

De Martin *et al.*[30] developed a new prognostic model to identify patients with acute severe autoimmune hepatitis (AS-AIH) who were not responsive to corticosteroid therapy, and who will need LT earlier. These authors found that patients with SURFASA score lower than -0.9 had 75% chances to respond to therapy, and patients with a score higher than 1.75 had 85-100% chances to die or receive a transplant.[30]

$$\text{SURFASA Score} = -6.80 + 1.92 \times (D_0\text{-INR}) + 1.94 \times (\Delta D_3\text{-INR}) + 1.64 \times (\Delta D_3\text{-Bilirubin})$$

Later, Lin *et al.*[31] found similar results applying SURFASA in predicting corticoid therapy responsiveness, but the authors suggested a cut-off value of -2.35, which is significantly lower than that used in De Martin *et al.*[30] study. This discrepancy could be explained by differences in fibrosis levels in both cohorts.[31]

Budd-Chiari Syndrome

Budd-Chiari syndrome is a rare disease resulting from obstruction of the hepatic venous outflow that typically presents with abdominal pain, jaundice and ascites, and may also evolve rapidly to ALF. Budd-Chiari syndrome represents 1-2% of ALF patients and despite improvements in mortality in recent years, it is still associated with an in-hospital mortality of almost 60%. An appropriate and timely management of these patients is, therefore, required.[32] Thuluvath *et al.*[32] found five risk factors associated with mortality: age ≥ 50 years, spontaneous bacterial peritonitis, sepsis, acute respiratory failure, and cancer. Based on these risk factors, the authors developed a short-term mortality prediction model (Rotterdam BCS Index) with a good accuracy (AUROC 0.76). However, these results could not be compared to other models and scores because of the way data were collected.[32]

Amanita phalloides Poisoning

Most deaths caused by mushroom poisoning are due to *Amanita phalloides*, which has two main toxins. Phallotoxin causes alteration in the cellular membrane of the enterocyte, whereas amatoxin causes protein synthesis inhibition in hepatocytes, leading to massive hepatocyte necrosis, and subsequent ALF.[33] Due to the poor outcome and the uncertainty related to LT in amatoxin poisoning, Ganzert *et al.* [34] performed a retrospective study looking for criteria to predict survival in these patients. The authors found that survival could be predicted using prothrombin index > 25% in combination with serum creatinine > 106 μmol/L between days 3 to 10 after ingestion, with a sensitivity of 100% and a specificity of 98%. Escudié *et al.*[33] performed a study with 27 patients with *Amanita phalloides* poisoning. The authors evaluated the criteria previously proposed by Ganzert *et al.*[34] and found less predictive power than KCC: acetaminophen and non-acetaminophen KCC were equally efficient identifying patients with poor outcome. They also found that 52% of the patients with prothrombin index < 25% did not need LT, suggesting that this threshold should be as lower as < 10% after day 4 of ingestion.[34] Interestingly, a shorter interval between mushroom consumption and the onset of diarrhoea was associated with fatal outcome.[33] These results were later confirmed in a small case series performed by Ferreira *et al.*[35].

5.3. Improving Prognostic Criteria

Serum Markers

Arterial blood lactate levels are elevated in ALF, because of (1) impaired hepatic clearance of lactate from circulation, and (2) simultaneous MOF, resulting in increased peripheral lactate production. For this reason, lactate seemed an attractive prognostic factor in ALF.[36] However, its use as a prognostic marker has been controversial. Bernal *et al.*[37] proposed the modified KCC by adding lactate levels to KCC, and found a greater accuracy when compared with KCC alone. More recent studies performed by MacQuillan *et al.*[38] and Schmidt *et al.*[25] found that modified KCC significantly reduced specificity to < 50%, and hyperlactatemia should be considered an independent prognostic marker. This variability of lactate levels prognostic significance could be explained by several factors, specially the timing and the volume of fluid resuscitation used.[25] Also, one-point time lactate measurement cannot predict survival in AALF, but persistent hyperlactatemia showed better results, thus emphasizing the importance of serial measurements.[36]

In a retrospective study, Hadem *et al.*[39] developed bilirubin-lactate-aetiology score (BiLe), which revealed better overall accuracy than MELD, and slightly better accuracy than KCC. Subsequently, Bernal *et al.*[40] found that BiLE had lower accuracy than KCC but recently, Figueira *et al.*[41] found a performance of BiLE score similar to that of Hadem *et al.*[39], suggesting that further research is needed to validate this score.

$$\text{BiLE Score} = \text{Bilirubin (μmol/L/100)} + \text{Lactate (mmol/L)} + 4 \text{ (if indeterminate ALF or Budd-Chiari syndrome)} - 2 \text{ (if AALF)}$$

Recently, Agrawal *et al.*[42] studied 50 ALF patients aiming to identify immune and laboratory parameters associated with spontaneous survival in ALF. The authors 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. After applying a logistic regression, the authors found that combined lactate and NK cell levels could predict survival with a sensitivity of 96% and a specificity of 79% (AUROC of 0.943).[42]

Serum phosphate is also linked to ALF. Hypophosphatemia is associated with spontaneous survival, and it is believed to be caused by hepatic regeneration processes, which consume phosphate. Hyperphosphatemia is associated with poor prognosis (renal impairment is a necessary condition to the development of hyperphosphatemia).[43] Despite the theoretical reasoning, clinical studies failed to demonstrate that phosphate could be used as a reliable prognostic marker in ALF.[38, 43, 44]

Antoniades *et al.*[45] found that actin-free group-specific component (AF-Gc) globulin levels were significantly lower in patients with ALF, and the extent of its reduction was related to the degree of organ dysfunction. Group-specific component (Gc) globulin is a multifunctional protein which is synthetized in the liver, binding and removing extracellular free actin released by necrotic cells. AF-Gc globulin levels were also lower in patients who did not survive or who underwent LT. Its isolated predictive value was lower than MELD score, even though it could be employed concomitantly with other clinical parameters.[45]

Imagiological Exams

Yamagishi *et al.*[46] reported that small liver volume was associated with poor prognosis in ALF. In this study, the authors used a computed tomography (CT) scan, which is a non-invasive technique, to determine estimated liver volume (ELV); they then compared it with standard liver volume (SLV, calculated using the patient body surface area). The authors found that not only could the ELV/SLV ratio estimate liver atrophy in ALF, but it was also significantly correlated to survival, with greater significance for ratios of 0.80 and 0.85 at the time of the onset of ALF.[46] These findings encouraged Yamagishi *et al.*[47] to develop a new prognostic model using ELV/SLV ratio.

$$Z = -2.6213 - (0.15234 \times \text{Bilirubin [mg/dL]}) + (4.5734 \times \text{ELV/SLV ratio})$$

Caution should be exercised when interpreting these results[46, 47], because there are substantial differences in the distribution of aetiologies of ALF between Western countries and Japan. It is also noteworthy that this study did not find that KCC was related to survival and this could also be explained by differences in aetiologies between Western countries and Japan, where the study took place.[46]

Indeed, a European study conducted by Zabron *et al.*[48] enrolled 273 patients with ALI and ALF. The authors found that 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.[48]

Recently Kuroda *et al.*[49] studied the potential utility of contrast-enhanced ultrasonography as a prognostic tool in ALF. The authors found that time-intensity curves reflect the hemodynamics of liver tissue. They also found that the interval between time to peak of hepatic artery and liver parenchyma had a better prognostic performance than MELD and KCC. However, this study had a small sample size, and only included one patient with AALF (the main cause of ALF in Western countries) and therefore, larger prospective clinical studies are needed.[49]

Asialoglycoprotein binds to its receptor exclusively on the surface of hepatocytes, and scintigraphy with Tc-99m GSA, which is a synthetic asialoglycoprotein which enables an evaluation of liver function in ALF patients.[50] Tatsumi *et al.*[50] found that Tc-99m GSA scintigraphy was significantly associated with 28-day mortality. These results were later supported by a study performed by Suzuki *et al.*[51]. 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.[50]

Indocyanine green (ICG) is a water-soluble dye that is taken up by hepatocytes; it is not metabolized, and it is excreted in bile, unchanged and with no enterohepatic recirculation. After being administered intravenously, it is eliminated by the liver, and can be used as a dynamic liver function test. ICG can be assessed using serial blood sampling, but also non-invasive techniques.[52] Merle *et al.*[53] found that ICG measurements were significantly lower in patients with ALF who did not recover spontaneously. Later, Feng *et al.*[54] developed a new model to predict outcome, which included MELD and ICG retention rate at 15 minutes (ICGR15) that measures ICG clearance, resulting in the ICGR15-MELD model. This model performed better than KCC; 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.[54]

$$\text{ICGR15-MELD Model} = 0.096 \times \text{ICGR15} + 0.174 \times \text{MELD score} - 9.346$$

Biomarkers Associated with Liver Regeneration

Biomarkers have been explored as potential tools for prognostic assessment, both alone or in combination with prognostic models based on clinical variables.[55] In ALF, recent advances have been made in the field of micro ribonucleic acid (miRNA) and also extracellular vesicles (particularly microvesicles).

miRNA are small non-coding ribonucleic acid (RNA) molecules containing about 22 nucleotides that function in RNA silencing and post-transcriptional regulation of gene expression.[55] 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, we should incorporate miRNA signatures to improve prognostic models or to develop new ones.[56] Salehi *et al.*[57] studied how miRNA signatures could be linked to liver regeneration and their potential role in AALF prognostic models. The authors found changes in serum miRNA profile of ALF 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, which shows that spontaneous recovery is associated with initiation of liver regeneration.[58] This miRNA profile is known to drive proliferation, innate immunity, and angiogenesis.[57] Subsequently, Tavabie *et al.*[56] studied how miRNA signature could improve outcome prediction models in AALF. After comparing miRNA expression in survivors and non-survivors, the authors used multiple logistic regression to develop a miRNA-based 21-day mortality outcome prediction model. The early time-point model contained miRNA-150 and -27a as continuous variables, and miRNA-149, -191 and -20a as categorical variables. The late time-point model contained miRNA-122 and -30a as continuous variables, and miRNA-149, -191 and 16-2 as categorical variables. 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.[56]

Extracellular vesicles are a heterogeneous group of membrane-bound vesicles that contain cell-derived biomolecules, such as proteins, lipids, RNA, and miRNA. They are often classified as exosomes, microvesicles, or apoptotic bodies, relatively to their size, density, and biochemical composition. Microvesicles, whose size range from 100-200 nm to 1 μm, are generated by plasma membrane budding. Hitherto, most studies compared patients with ALI to healthy controls, thus limiting their clinical relevance[59] with the exception of a study conducted by Stravitz *et al.*[60], in 2013. In a previous study, Stravitz *et al.*[61] evaluated the effects of ALI and ALF in coagulation using thromboelastography. They found that clot formation in patients with ALF was normal, and anticoagulant levels were markedly reduced, which could explain why thrombotic complications were more common than bleeding complications, despite the high levels of INR. These results supported further investigation by Stravitz *et al.*[60] attempting to understand the role of microparticles in coagulation, particularly procoagulant microparticles expressing tissue factor, and how they could affect systemic complications and adverse outcome in ALF. In this study, the authors observed higher microvesicles levels in patients with systemic inflammatory response syndrome (SIRS), and high-grade HE. They also found that microparticles with a size ranging from 0.28 μm to 0.64 μm were associated with 21-day outcome of ALI/ALF.[60]

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 patients with ALF.

5.4. Futility of Liver Transplantation in Acute Liver Failure

Clinicians have not yet found an ideal prognostic model to select patients with ALF 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; however, this preference 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 has not been an accurate definition for futility in LT.[9] Several identified factors are responsible for influencing patient survival, such as: (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.[62]

Barshes *et al.*[63] created a score 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 (mechanical ventilation or hemodynamic support); (2) age > 50 years; (3) BMI $\geq$ 30 Kg/m^2; (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%.[63]

Bernal *et al.*[62] analysed data from 1379 patients with ALF and grade 3 or 4 of 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. One 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 patients with ALF, but also that death was more common in patients with acetaminophen-related aetiology, use of vasopressor therapy and blood groups other than A. These data reinforce the importance of aetiology in the clinical outcome of these patients, with AALF associated with more severe disease. However, paradoxically patients with AALF not listed for LT had better survival than other causes of ALF.[62]

Germani *et al.*[5] analysed data from 4903 adult patients with ALF who received LT between 1988 and 2009. The authors found an improvement in survival rate after LT over time, despite the increasing donor age, which reflects a worldwide trend. A graft donor age above 60 years is a well-established adverse factor for LT. However, this was counter-balanced by an improvement in pre-, intra- and post-operative patient care. Improvements in survival could not be attributed only to one factor, since new immunosuppressor agents, as well as better anaesthetic and intensive care management also played a role in these results. After performing a multivariable analysis, the authors suggested that LT should be avoided in patients who have a high risk of 1-year death or high risk of liver failure, particularly male patients older than 50 who use grafts from donors older than 60 years, ABO mismatching and a reduced size graft.[5]

Besides developing a score to predict which patients would benefit the most from LT, Frigorilli *et al.*[29] also analysed ALF-OFs to predict mortality after LT and its potential in identifying futile LT in patients with AALF. This new score (cut-off value of 8.5) had a good performance in predicting futility of LT in AALF, with high sensitivity (100%) and acceptable specificity (79.2%). Therefore, using ALF-OFs

in patients with AALF allowed the subdivision 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).[29]

Survival after LT in ALF has increased in recent years, although it is not comparable with survival in elective transplantation. 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 patients with ALF (on average, patients with ALF received LT four days after being included in the waiting list).[9] Although the studies of Barshes *et al.*[63] and Bernal *et al.*[62] provide an insight into the risk factors associated with mortality in patients on the waiting list or after LT, it did not provide a practical guidance about decision making regarding the patient. The results of Germani *et al.*[5] are encouraging, but need to be confirmed by further investigation.

5.5. 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 (secondary to impaired hepatic clearance). This principle is known as the toxin and albumin hypothesis.[8] Besides its oncotic pressure effect, albumin can be used as a binding and scavenging molecule to remove toxins from blood[64], under the assumption that removing these toxins from plasma will improve clinical state and outcome in ALF.[65] This principle was incorporated in albumin-based artificial ECLS, which are based on adsorption and filtration principles, and classified according to: (1) membrane type/porosity/selectivity; (2) types of columns filters; (3) modality of RRT used; (4) need to have an albumin enriched dialysate; (5) extracorporeal volume required. Based on these features, artificial ECLS are divided in two groups: dialysis-based techniques (i.e., MARS, SPAD and HDF) and plasma adsorption techniques (i.e., HV-TPE, FPSA and hemoadsorption).[64]

Molecular adsorbent recirculating system (MARS) was first developed by Stange and colleagues in 1993, though the features of this technique have been subsequently refined. 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 fiber membrane.[66] This membrane has polymer-attached albumin which displays higher-affinity creating a concentration gradient for serum toxins.[8] Albumin serves as the dialysate solution, which is regenerated by flowing through two adsorbent columns (i.e., anion exchange column, uncoated charcoal column) and a second dialyzer, removing water-soluble and albumin-binding toxins from patient blood. The second dialyzer acts as a haemodialysis module restoring hydroelectrolytic, acid-base and glucose balances, and removing water-soluble substances.[66] Hollow fiber membrane has a small pore size preventing

molecules with a molecular weight greater than 50 KDa (i.e., essential hormones and growth factors) from crossing the membrane and be removed from patient's blood.[8]

Kantola *et al.*[67] performed a controlled single-centre study, involving 159 patients with ALF, to determine the effect of MARS on survival. 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%). Survival in patients with toxic causes of ALF was not evaluated because clinical baseline parameters were significantly different.[67]

Saliba *et al.*[68] performed the unique randomized, controlled, multicentre trial which enrolled 102 patients with ALF, 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 survival post-LT was higher than expected, which could be explained by better medical and surgical management, as well as lower mean time between randomization and LT (16 hours). However, in the subgroup analysis, the authors found that MARS improved transplant-free survival both in patients with AALF and those who received three or more MARS treatment sessions.[68]

Gerth *et al.*[69] performed a case-control study with 53 patients with ALI. The authors 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, which corroborates previous findings that MARS enables liver function stabilization and promotes liver regeneration.[69]

Recently, Camus *et al.*[70] published results from a national multicentre study with the treatment of different liver conditions using MARS. This study included 129 patients with ALF, and found that MARS improved survival in acetaminophen-related aetiologies and in those patients who received more than three sessions of MARS treatment, reinforcing the results previously found by Saliba *et al.*[68]

Although larger randomized and controlled studies with MARS failed to demonstrate clear improvement in survival in patients with ALF, smaller case series have shown that MARS plays an important role in improving clinical and laboratorial parameters in ALF. Schmidt *et al.*[71] found that MARS has beneficial hemodynamic effects, as it increases arterial blood pressure and systemic vascular resistance, and decreases heart rate. This suggests that MARS can remove albumin-binding vasoplegic factors that cause hypotension, reinforcing the toxin hypothesis. MARS treatment was generally well-tolerated, although one case of dialysis-induced hypotension was reported.[71]

Unlike MARS, single-pass albumin dialysis (SPAD), uses a single conventional continuous RRT machine, without the need for additional columns/filters. Patient blood is dialyzed against an albumin dialysate solution across a permeable high-flux membrane.[8]

Karvellas *et al.*[72] performed a case-control study to evaluate the impact of SPAD in patients with ALF. They found that this technique is safe, but did not improve clinical and laboratorial parameters, such as HE grade, systemic hemodynamics, and laboratory values.

Later, Sponholz *et al.*[73] performed a prospective, randomized crossover study with 32 patients with liver failure (18 patients with ACLF, 9 patients with ALF, 5 patients with liver graft failure). This study aimed to compare clinical and laboratory parameters between treatment with SPAD and MARS. Both

systems 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. As demonstrated in other studies, the authors hypothesized that SPAD efficiency could be improved by increasing dialysate flow rate (700 mL/hour in this study) and/or increasing treatment time; moreover, it will reduce SPAD costs when compared with MARS.[73] In order to address this issue, Schmuck *et al.*[74] studied how SPAD could be more effective in ALF treatment. The authors found that dialysate flow rates lower than 700 mL/hour were less effective in removing albumin-binding toxins, and bile acids detoxification reached a maximum at a dialysate flow of 1000 mL/hour. However, increasing dialysate flow rates not only has technical limitations, but also increases treatment costs.[74]

Haemodialysis is a diffusion-based technique that removes low-weight molecules effectively. However, it shows lower efficacy in removing larger molecules. Therefore, a convection-based technique (hemofiltration) was developed to improve removal of larger solutes in patients with renal failure. Later, the combination of diffusion and convection techniques resulted in hemodiafiltration (HDF).[75] Fujiwara *et al.*[76] performed a comparative study of therapeutic plasma exchange (TPE) and high-volume filtrate HDF and high-flow dialysate continuous HDF. This nationwide survey found that both HDF techniques had higher rates of restoration of consciousness in patients with ALF. However, this study did not find significant differences in survival between the various ECLS methods. Furthermore this study lacked a control group to understand the impact of these therapeutics on overall survival.[76] Takikawa *et al.*[77] 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.[77]

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 (or 8-12 L of plasma per procedure). 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 patients with ALF.[78]

Larsen *et al.*[78] performed a clinical trial to study the effect of HV-TPE on survival and the effect in immune response. 182 patients presenting with ALF were included and the authors found that 3-month survival only improved in patients who had received HV-TPE, but who had not received LT when compared with SMT.[78] Similarly to Saliba *et al.*[68], 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. In this study, monocyte and neutrophil counts did not differ between pre- and post-HV-TPE. However, the authors found a significant reduction in circulating damage associated molecular patterns (DAMPs, i.e., histone-associated DNA), 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 SOFA scores. For this reason, the authors hypothesized that HV-TPE modulates migratory capabilities of circulating innate immune cells, decreasing the liver insult and MOF.[78]

Recently Maiwall *et al.*[79] performed a randomized controlled study using standard TPE in 40 patients with NAALF and cerebral oedema. This study demonstrated that standard TPE is associated with improvement of 21-day transplant-free survival. The authors considered that TPE in higher volumes, such as HV-TPE used by Larsen *et al.*[78], 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, such as levels of bilirubin, INR, and lactate. Standard TPE reduced DAMPs, endotoxins, and proinflammatory cytokines, and restored monocyte phagocytic function. 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.[79]

Fractionated plasma separation and adsorption (FPSA, Prometheus®) is an ECLS system in which patient plasma is separated through an albumin-permeable filter with a molecular weight cut-off of 250 KDa. This fractionated plasma containing patient albumin flows through a neutral resin adsorber and an anion-exchange column, before returning to circulation, thus removing albumin-binding toxins and other metabolites. The blood also flows through another circuit, where it is treated by high-flux haemodialysis, removing water-soluble toxins.[64] Until now, randomized controlled studies evaluating the impact of FPSA on survival of patients with ALF have not been carried out, only not controlled studies with a small number of patients. Several case series have repeatedly demonstrated that FPSA has a beneficial role in improving clinical and laboratory parameters, thus decreasing levels of bilirubin, ammonia, aminotransferases, blood urea, creatinine, and HE. FPSA also improved acid-base and water-electrolytes disorders, as well as hemodynamic stability.[80-82] Rocen *et al.*[83] demonstrated that FPSA had a beneficial effect on improving laboratory parameters, and it could also reduce the TNF-α and inflammation markers (i.e., C reactive protein, procalcitonin). Grodzicki *et al.*[84] also showed similar improvements in laboratory parameters. They estimated that the mortality rates with SMT+FPSA+LT, SMT+FPSA, and SMT alone were 33%, 68%, and > 90%, respectively.

Hemoadsorption (CytoSorb®) uses an adsorption column to adsorb molecules with a molecular weight lower than 55 KDa, which was primarily used to treat sepsis.[85] Dhokia *et al.*[85] reported two cases of ALF successfully treated using CytoSorb®, thus reducing bilirubin and bile acids levels significantly. Recently, Tomescu *et al.*[86] performed a prospective study including 28 patients and showed a significant reduction in bilirubin, creatinine, ammonia, and C reactive protein. The authors also showed that a decrease in SOFA score after CytoSorb® therapy was correlated to better outcomes. The main side effect reported was thrombocytopenia, although it was not associated with higher rates of bleeding disorders. The improvement in biochemical parameters using this technique is promising, although more studies are needed in order to produce robust evidence of improvement in survival.[86]

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, mimicking detoxification and synthetic functions of the liver. Current bioreactors can incorporate human (ELAD) or porcine hepatocytes (HepatAssist).[8]

Extracorporeal liver assist device (ELAD) is a bioartificial ECLS that incorporates human hepatoblastoma cells in a dialysis cartridge.[87] Ellis *et al.*[87] performed a pilot controlled study with 24 patients with ALF, 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 also showed evidence of improvement in some clinical findings, such HE, albeit not statistically significant. ELAD also influenced spontaneous recovery in approximately 13% of patients who were listed for, but did not received LT.[87]

HepatAssist is a porcine hepatocyte-based bioartificial ECLS.[88] Demetriou *et al.*[88] performed a large prospective, randomized, controlled, multicentre study to evaluate HepatAssist system in 171 patients with ALF (24 of whom experienced primary nonfunction following LT). The authors found no significant differences on 30-day survival between the two groups; however, there was a trend toward survival in patients treated with HepatAssist. One of the most influential predictors for this result was LT. 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 times for an available graft for LT.[88]

6. CONCLUSIONS

This study concludes that a lack of uniformization of selection criteria for LT in patients with ALF remains until today. KCC continue to be the most used criteria to select patients with ALF for LT in Europe, although previous studies have shown their limited sensitivity. In recent years, several serum and even imagiological 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, very 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. Today, accurate selection of patients with ALF 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 and new therapeutic targets. 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.

Another conclusion drawn from this review is the 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 should be considered vital.

We conclude that 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 patients with AFL was improved. Artificial liver support systems showed more promising results than bioartificial systems. Particularly, the studies which included MARS suggested that this technique can be used as a “bridge” therapeutic modality to LT in patients with ALF. We propose that new studies should be carried out in order to evaluate MARS as a “bridge” therapy. 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.

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8. REFERENCES

1. Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis. 1970;3:282-98.

2. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993;342(8866):273-5.

3. Stravitz RT, Lee WM. Acute liver failure. Lancet. 2019;394(10201):869-81.

4. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369(26):2525-34.

5. 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.

6. Wendon J, Cordoba J, Dhawan A, Larsen FS, Manns M, Samuel D, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66(5):1047-81.

7. Struecker B, Raschzok N, Sauer IM. Liver support strategies: cutting-edge technologies. Nat Rev Gastroenterol Hepatol. 2014;11(3):166-76.

8. 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.

9. O'Grady J. Timing and benefit of liver transplantation in acute liver failure. J Hepatol. 2014;60(3):663-70.

10. 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.

11. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989;97(2):439-45.

12. 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.

13. 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.

14. 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.

15. 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-e45.

16. Bismuth H, Samuel D, Castaing D, Adam R, Saliba F, Johann M, et al. Orthotopic liver transplantation in fulminant and subfulminant hepatitis. The Paul Brousse experience. Ann Surg. 1995;222(2):109-19.

17. Izumi S, Langley PG, Wendon J, Ellis AJ, Pernambuco RB, Hughes RD, et al. Coagulation factor V levels as a prognostic indicator in fulminant hepatic failure. Hepatology. 1996;23(6):1507-11.

18. 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.

19. 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.

20. Kremers WK, van IM, Kim WR, Freeman RB, Harper AM, Kamath PS, et al. MELD score as a predictor of pretransplant and posttransplant survival in OPTN/UNOS status 1 patients. Hepatology. 2004;39(3):764-9.

21. 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.

22. Craig DG, Reid TW, Wright EC, Martin KG, Davidson JS, Hayes PC, et al. The sequential organ failure assessment (SOFA) score is prognostically superior to the model for end-stage liver disease (MELD) and MELD variants following paracetamol (acetaminophen) overdose. Aliment Pharmacol Ther. 2012;35(6):705-13.

23. Craig DG, Zafar S, Reid TW, Martin KG, Davidson JS, Hayes PC, et al. The sequential organ failure assessment (SOFA) score is an effective triage marker following staggered paracetamol (acetaminophen) overdose. Aliment Pharmacol Ther. 2012;35(12):1408-15.

24. Cholongitas E, Theocharidou E, Vasianopoulou P, Betrosian A, Shaw S, Patch D, et al. Comparison of the sequential organ failure assessment score with the King's College Hospital criteria and the model for end-stage liver disease score for the prognosis of acetaminophen-induced acute liver failure. Liver Transpl. 2012;18(4):405-12.

25. Schmidt LE, Larsen FS. Prognostic implications of hyperlactatemia, multiple organ failure, and systemic inflammatory response syndrome in patients with acetaminophen-induced acute liver failure. Crit Care Med. 2006;34(2):337-43.

26. Bernal W, Wang Y, Maggs J, Willars C, Sizer E, Auzinger G, et al. Development and validation of a dynamic outcome prediction model for paracetamol-induced acute liver failure: a cohort study. Lancet Gastroenterol Hepatol. 2016;1(3):217-25.

27. Koch DG, Tillman H, Durkalski V, Lee WM, Reuben A. Development of a Model to Predict Transplant-free Survival of Patients With Acute Liver Failure. Clin Gastroenterol Hepatol. 2016;14(8):1199-206.e2.

28. 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.

29. 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.

30. De Martin E, Coilly A, Chazouillères O, Roux O, Peron JM, Houssel-Debry P, et al. Early liver transplantation for corticosteroid non-responders with acute severe autoimmune hepatitis: The SURFASA score. J Hepatol. 2021;74(6):1325-34.

31. Lin S, Hall A, Kumar R, Quaglia A, Jalan R. Validation of the SURFASA score to define steroid responsiveness in patients with acute autoimmune hepatitis. J Hepatol. 2021.

32. Thuluvath PJ, Alukal JJ, Zhang T. Acute liver failure in Budd-Chiari syndrome and a model to predict mortality. Hepatol Int. 2021;15(1):146-54.

33. Escudié L, Francoz C, Vinel JP, Moucari R, Cournot M, Paradis V, et al. Amanita phalloides poisoning: reassessment of prognostic factors and indications for emergency liver transplantation. J Hepatol. 2007;46(3):466-73.

34. Ganzert M, Felgenhauer N, Zilker T. Indication of liver transplantation following amatoxin intoxication. J Hepatol. 2005;42(2):202-9.

35. Ferreira R, Romãozinho JM, Amaro P, Ferreira M, Sofia C. Assessment of emergency liver transplantation criteria in acute liver failure due to Amanita phalloides. Eur J Gastroenterol Hepatol. 2011;23(12):1226-32.

36. Bernal W. Lactate is important in determining prognosis in acute liver failure. J Hepatol. 2010;53(1):209-10.

37. Bernal W, Donaldson N, Wyncoll D, Wendon J. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. Lancet. 2002;359(9306):558-63.

38. Macquillan GC, Seyam MS, Nightingale P, Neuberger JM, Murphy N. Blood lactate but not serum phosphate levels can predict patient outcome in fulminant hepatic failure. Liver Transpl. 2005;11(9):1073-9.

39. Hadem J, Stiefel P, Bahr MJ, Tillmann HL, Rifai K, Klempnauer J, et al. Prognostic implications of lactate, bilirubin, and etiology in German patients with acute liver failure. Clin Gastroenterol Hepatol. 2008;6(3):339-45.

40. Bernal W, Auzinger G, Wendon J. Prognostic utility of the bilirubin lactate and etiology score. Clin Gastroenterol Hepatol. 7. United States2009. p. 249; author reply

41. Figueira ERR, Rocha-Filho JA, Lanchotte C, Nacif LS, de Paiva Haddad LB, Assalin AR, et al. Creatinine-lactate score predicts mortality in non-acetaminophen-induced acute liver failure in patients listed for liver transplantation. BMC Gastroenterol. 2021;21(1):252.

42. 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.

43. Schmidt LE, Dalhoff K. Serum phosphate is an early predictor of outcome in severe acetaminophen-induced hepatotoxicity. Hepatology. 2002;36(3):659-65.

44. Bernal W, Wendon J. More on serum phosphate and prognosis of acute liver failure. Hepatology. 38. United States2003. p. 533-4.

45. Antoniades CG, Berry PA, Bruce M, Cross TJ, Portal AJ, Hussain MJ, et al. Actin-free Gc globulin: a rapidly assessed biomarker of organ dysfunction in acute liver failure and cirrhosis. Liver Transpl. 2007;13(9):1254-61.

46. Yamagishi Y, Saito H, Tada S, Horie Y, Kato S, Ishii H, et al. Value of computed tomography-derived estimated liver volume/standard liver volume ratio for predicting the prognosis of adult fulminant hepatic failure in Japan. J Gastroenterol Hepatol. 2005;20(12):1843-9.

47. Yamagishi Y, Saito H, Ebinuma H, Kikuchi M, Ojiro K, Kanamori H, et al. A new prognostic formula for adult acute liver failure using computer tomography-derived hepatic volumetric analysis. J Gastroenterol. 2009;44(6):615-23.

48. 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.

49. Kuroda H, Abe T, Fujiwara Y, Nagasawa T, Suzuki Y, Kakisaka K, et al. Contrast-Enhanced Ultrasonography-Based Hepatic Perfusion for Early Prediction of Prognosis in Acute Liver Failure. Hepatology. 2021;73(6):2455-67.

50. 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.

51. 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.

52. Halle BM, Poulsen TD, Pedersen HP. Indocyanine green plasma disappearance rate as dynamic liver function test in critically ill patients. Acta Anaesthesiol Scand. 2014;58(10):1214-9.

53. Merle U, Sieg O, Stremmel W, Encke J, Eisenbach C. Sensitivity and specificity of plasma disappearance rate of indocyanine green as a prognostic indicator in acute liver failure. BMC Gastroenterol. 2009;9:91.

54. 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.

55. De Clercq P, Geerts A, Van Vlierberghe H, Verhelst X. The utility of biomarkers in prognosis assessment of patients with acute liver failure. Hepatol Res. 2021;51(7):750-7.

56. 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.

57. 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.

58. 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.

59. Thietart S, Rautou PE. Extracellular vesicles as biomarkers in liver diseases: A clinician's point of view. J Hepatol. 2020;73(6):1507-25.

60. 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.

61. Stravitz RT, Lisman T, Luketic VA, Sterling RK, Puri P, Fuchs M, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. J Hepatol. 2012;56(1):129-36.

62. 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.

63. 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.

64. 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.

65. Larsen FS. Artificial liver support in acute and acute-on-chronic liver failure. Curr Opin Crit Care. 2019;25(2):187-91.

66. 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.

67. 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.

68. 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.

69. 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.

70. 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.

71. 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.

72. 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.

73. 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.

74. 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.

75. Tattersall JE, Ward RA. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013;28(3):542-50.

76. 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.

77. 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.

78. 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.

79. 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. 2021.

80. 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.

81. 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.

82. 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.

83. Rocen M, Kieslichova E, Merta D, Uchytilova E, Pavlova Y, Cap J, et al. The effect of Prometheus device on laboratory markers of inflammation and tissue regeneration in acute liver failure management. Transplant Proc. 2010;42(9):3606-11.

84. 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.

85. 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.

86. 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.

87. 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.

88. 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 7-70.

APPENDIX I. Sensitivity and specificity of prognostic criteria used in acute liver failure of included studies

Study	Years Included in the Study	Criteria	Aetiology	Number of Patients	Sensitivity (%)	Specificity (%)	AUROC	Comment
Craig *et al.*[10], 2011	2003-2009	SOFA	Singe-time point AOD	100	95 (79-99)	71 (66-72)	0.92 (0.86-0.98)	>7 by 96h post-overdose
Craig *et al.*[12], 2010	1973-2007	KCC	AALF	1960	58 (53-63)	95 (93-96)	0.91 (0.79-0.99)	-
Bailey *et al.*[13], 2003	1989-2000	KCC	AALF	880	69 (63-75)	92 (81-97)	0.61 (0.55-0.67)	-
McPhail *et al.*[14], 2010	1975-2009	KCC	NAALF	1105	68 (59-77)	82 (75-88)	0.855	-
McPhail *et al.*[15], 2016	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.*[18], 2015	1997-2010	Clichy	All	173	71	53	-	LT patients excluded
			AALF	-	75	56	-	
			NAALF	-	69	50	-	

APPENDIX I. (continued)

Study	Years Included in the Study	Criteria	Aetiology	Number of Patients	Sensitivity (%)	Specificity (%)	AUROC	Comment
Schmidt *et al.*[19], 2007	1999-2004	MELD	AALF	124	60	69	0.58 (0.47-0.69)	At day 1 of HE
Bechmann *et al.*[21], 2010	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
Craig *et al.*[22], 2012	2003-2010	SOFA	Singe-time point AOD	138	96 (82-100)	73 (63-81)	0.919 (0.860-0.959)	>7 by 92h post-overdose
		MELD			86 (67-96)	71 (62-79)	0.808 (0.733-0.870)	>42 by 92h post-overdose
Craig *et al.*[23], 2012	2005-2011	SOFA	Staggered AOD	50	100 (77-100)	58 (41-75)	0.87 (0.73-0.96)	>5 at admission
					92 (64-100)	83 (66-93)	0.94 (0.83-0.99)	>10 by 24h post-admission
					100 (54-100)	97 (83-99)	0.98 (0.84-1.00)	>13 by 48h post-admission
Cholongitas *et al.*[24], 2012	1993-2010	KCC	AALF	102	57	86	0.71	LT patients excluded
		MELD			88	30	0.61	

APPENDIX I. (continued)

Study	Years Included in the Study	Criteria	Aetiology	Number of Patients	Sensitivity (%)	Specificity (%)	AUROC	Comment
Cholongitas *et al.*[24], 2012	1993-2010	SOFA	AALF	102	71	79	0.84	LT patients excluded
Schmidt *et al.*[25], 2006	1999-2004	KCC	AALF	95	71	77	-	-
		Modified KCC		91	91	40	-	
Bernal *et al.*[26], 2016	2000-2014	Dynamic Day 1 Model	AALF	412	-	-	0.91 (0.87-0.94)	External validation set
		Dynamic Day 2 Model			-	-	0.91 (0.88-0.95)	
Kock *et al.*[27], 2016	1998-2013	ALFSG Model	AALF	1974	-	-	0.84	Prediction of survival at 21-day
Rutherford *et al.*[28], 2012	1998-2011	ALFSG-PI	All	500	86	65	0.822	-
			AALF	-	81	78	-	
			NAALF	-	85	60	-	
Frigorilli *et al.*[29], 2017	1990-2015	ALF-OFs	AALF	-	83	83	0.890	5.58 cut-off value
		KCC			87	40	0.654	-
De Martin *et al.*[30], 2021	2009-2016	SURFASA	AIH	83	84	88	0.93 (0.88-0.98)	-0.9 cut-off value

APPENDIX I. (continued)

Study	Years Included in the Study	Criteria	Aetiology	Number of Patients	Sensitivity (%)	Specificity (%)	AUROC	Comment
Lin *et al.*[31], 2021	2010-2019	SURFASA	AIH	19	100	92	0.96	-2.35 cut-off value
Bernal *et al.*[37], 2002	1999-2000	Modified KCC	AALF	99	91	94	-	Validation cohort
Hadem *et al.*[39], 2008	1996-2005	MELD	All	101	65	69	0.71 (0.61-0.82)	32 cut-off value
		BiLE		101	79	84	0.87 (0.80-0.95)	6.9 cut-off value
Bernal *et al.*[40], 2009	1999-2007	KCC	All	266	69	90	-	LT patients excluded
		BiLE			53	89	-	Excluded LT 6.9 cut-off value
Figueira *et al.*[41], 2021	-	Creatinine-lactate score	NAALF	100	87	71	0.835 (0.748-0.923)	179.51 cut-off value
		MELD			61	78	0.697 (0.587-0.807)	44 cut-off value
		BiLE			70	84	0.814 (0.719-0.909)	11.02 cut-off value

APPENDIX I. (continued)

Study	Years Included in the Study	Criteria	Aetiology	Number of Patients	Sensitivity (%)	Specificity (%)	AUROC	Comment
Schmidt *et al.*[43], 2002	1999-2000	Serum Phosphate	AOD	16	89	100	-	> 1.2 mmol/L
		KCC		15	67	97	-	-
		Serum Phosphate and KCC		20	94	97	-	-
Bernal *et al.*[44], 2003	1998-2000	Serum Phosphate	AOD	55	81	89	-	LT patients excluded
		KCC		47	83	97	-	
		Serum Phosphate and KCC		65	94	86	-	
Kuroda *et al.*[49], 2021	2015-2019	KCC	All	50	56 (34-75)	91 (70-97)	0.731 (0.602-0.860)	-
		MELD			83 (60-95)	56 (34-77)	0.816 (0.693-0.939)	20 cut-off value
		TI (HA, LP) in CEUS			94 (71-100)	91 (75-97)	0.953 (0.895-0.998)	6.897 cut-off value
Merle *et al.*[53], 2009	2006-2007	ICG-PDR	All	25	86 (42-99)	89 (64-98)	0.90	≤ 6.3%/min cut-off value on day 1

APPENDIX I. (continued)

Study	Years Included in the Study	Criteria	Aetiology	Number of Patients	Sensitivity (%)	Specificity (%)	AUROC	Comment
Feng *et al.*[54], 2014	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; AIH: autoimmune hepatitis; ALF: acute liver failure; ALFSG-PI: Acute Liver Injury Study Group prognostic index; AOD: acetaminophen overdose; AUROC: area under the receiving operating characteristic; BiLE: bilirubin-lactate-aetiology score; CEUS: contrast-enhanced ultrasonography; HE: hepatic encephalopathy; ICG-PDR: indocyanine green plasma disappearance rate; 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; SOFA: sequential organ failure assessment; TI (HA, LP): time interval between time to peak of hepatic artery and liver parenchyma.