

ACUTE LIVER FAILURE: A DANGEROUS AND CHALLENGING SYNDROME

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Disclosure: No potential conflict of interest.

Received: 19.12.13 **Accepted:** 05.03.14

Citation: EMJ Hepatol. 2014;1:91-98.

ABSTRACT

Despite progress in understanding the underlying mechanisms, acute liver failure (ALF) is still one of the major clinical challenges in hepatology. A wide variety of aetiologies, and similarly, variable courses of the disease, make it crucial to identify the cause of ALF in each individual patient. Conservative therapy is only available for some patients; for many others, liver transplantation remains the only curative option for ALF. Thus, early evaluation and prognostication of the ALF syndrome is warranted for a timely decision to list a patient for transplantation or even as high urgency. This review aims to compose our current knowledge on epidemiology, mechanisms, and prognosis in ALF, and to give a perspective for future studies in this field.

Keywords: Acute liver failure, drug-induced liver injury (DILI), clinical management, cell death, prognosis.

DEFINITION

Sudden severe liver dysfunction in previously apparently healthy individuals is referred to as acute liver failure (ALF). ALF is characterised by rapid and massive hepatocellular death¹ and in many cases takes a life-threatening course, with liver transplantation (LTx) the only therapeutic option. In 1970, Trey and Davidson² defined fulminant hepatitis as a potentially reversible condition with occurrence of hepatic encephalopathy within 8 weeks of symptom onset.

Based on this first definition, the clinical hallmark of ALF is coagulopathy (International Normalised Ratio, INR ≥ 1.5) and hepatic encephalopathy in obviously healthy subjects.³ The exclusion of pre-existing liver diseases is important for the current definition of ALF; however, this cannot be achieved in all cases. More than 50% of Europeans are overweight, which is often associated with fatty liver, a serious liver disease.⁴ As such, it would be challenging to diagnose ALF in these individuals, who may have the underlying metabolic syndrome or fatty liver disease. A

more appropriate definition than ALF for patients with underlying chronic liver diseases (alcoholic hepatitis, chronic hepatitis B and C virus [HBV/HCV], autoimmune hepatitis, non-alcoholic fatty liver disease [NAFLD]), but without liver cirrhosis, would be acute-on-chronic liver failure (AOC-LF). The third main group of liver failure patients are those with acute-on-cirrhosis liver failure (AOCi-LF). These separated definitions may be more appropriate as the management and the outcomes differ in each group (Figure 1). Some patients with ALF have the possibility to recover without LTx. However, in patients with AOC or AOCi liver failure, the recovery after acute injury is unlikely and LTx is warranted.

With progressive loss of hepatic function, ALF leads to hepatic encephalopathy, coagulopathy, and multi-organ failure within a short period of time. Established specific therapy regimens and the introduction of LTx have improved the prognosis for some aetiologies; however, the overall mortality rate remains high.⁵ ALF accounts for approximately 6-8% of LTx procedures in the US and Europe.⁶ The accurate and timely diagnosis of

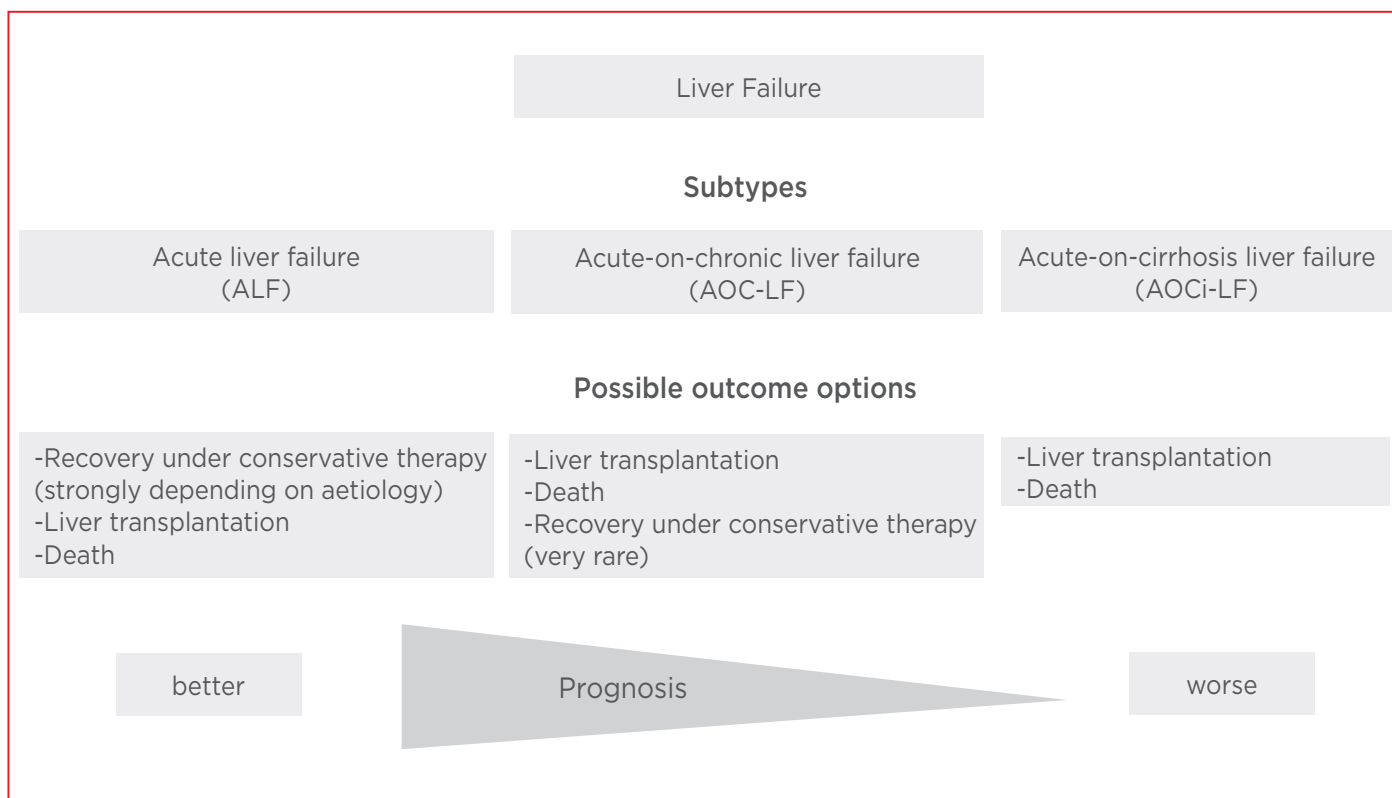


Figure 1: Diagram of liver failure subtypes, possible outcome, and clinical course.

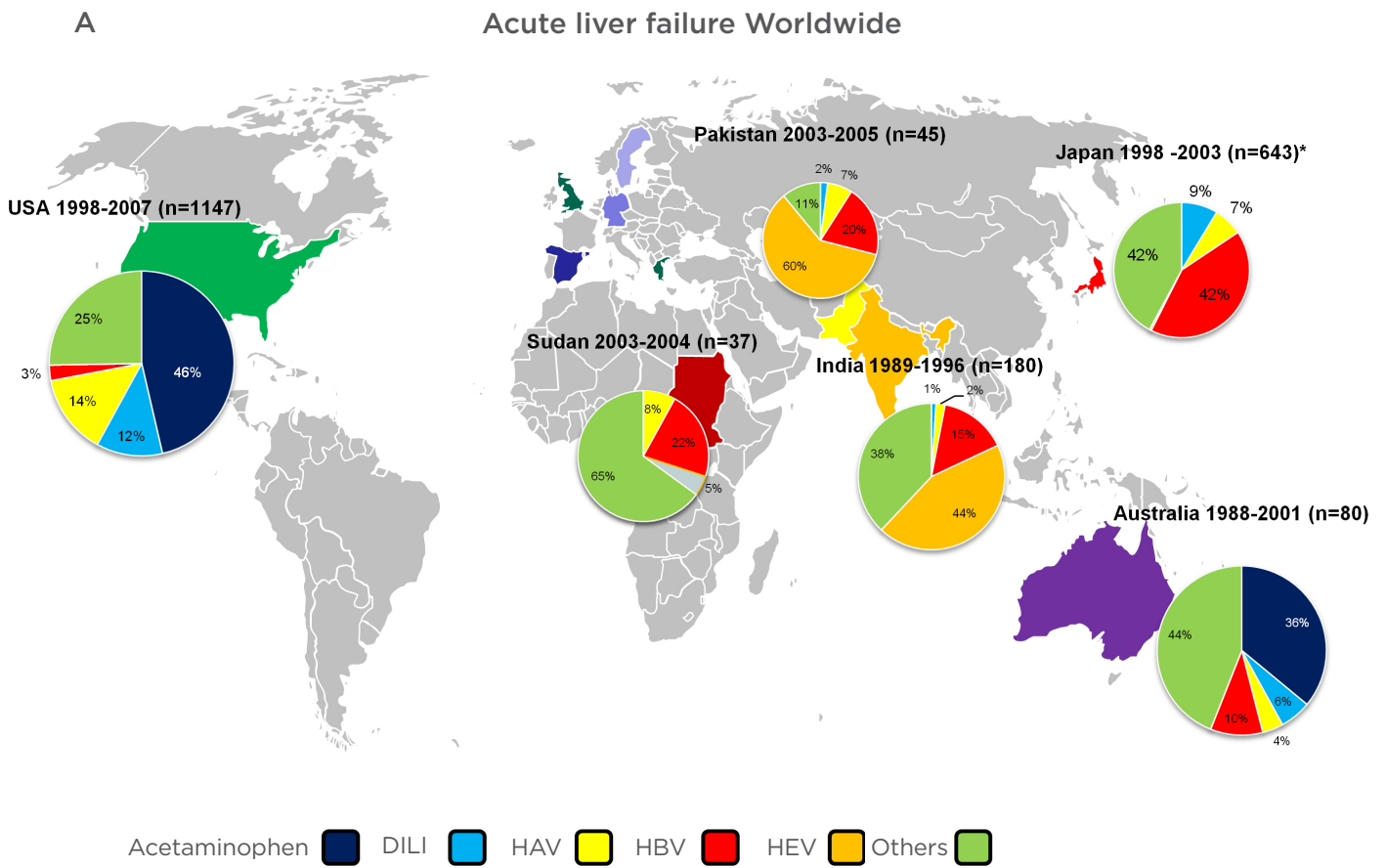
ALF, rapid identification of the underlying cause, transfer of the patient to a specialised transplant centre and, if applicable, initiation of a specific therapy and evaluation for LTx are crucial in current ALF management. Therefore, we focus here on epidemiology and molecular mechanisms, as well as novel tools, to predict the outcome in ALF.

EPIDEMIOLOGY AND AETIOLOGIES

ALF is a rare condition with multiple causes and varying clinical courses, and the exact epidemiologic data is scarce. The overall incidence of ALF is 1-6 cases per million people each year.⁵ Recent data from the US,⁷ the UK,⁸ Sweden,⁹ and Germany^{10,11} reveal drug toxicity as the main cause of ALF, followed by viral hepatitis and seronegative hepatitis (i.e. unknown or uncertain aetiology). In contrast, in the Mediterranean, Asia, and Africa, viral hepatitis is the leading cause of ALF.¹²⁻¹⁵ In addition to HBV, recent data indicate that hepatitis E virus (HEV) is more common than previously considered. Indeed, the incidence of HEV-induced liver injury in Europe appears to be increasing.¹⁶⁻¹⁸ An estimate of worldwide distribution and a comprehensive list of possible aetiologies of ALF are listed in [Figure 2](#) and [Table 1](#), respectively.

Despite being the leading cause of ALF in Western societies, the actual incidence of drug-induced liver injury (DILI) varies significantly among individual countries. For example, DILI in the general population was estimated at 1-2 cases per 100,000 person years,¹⁹ but this is much higher in Germany, where DILI accounts for approximately 40% of ALF.¹¹ As a structured medical history may be difficult in some cases, a standardised clinical management to identify the cause of DILI and optimise specific treatment has been proposed.²⁰ This includes assessment of clinical and laboratory features, determining the type of liver injury (hepatocellular versus cholestatic). Furthermore, to identify a cause, one must distinguish between a dose-dependent and an idiosyncratic (immune-mediated hypersensitivity) type of liver injury.²

Acetaminophen intoxication, as discussed in detail below, is the classic example of a direct, dose-dependent intoxication with acute hepatocellular necrosis.²¹ However, the vast majority of DILI are idiosyncratic reactions with a latency period of up to 1 year after initiation of treatment. Drugs that induce idiosyncratic DILI include antibiotics (amoxicillin/clavulanate, macrolides, nitrofurantoin, isoniazid), antihypertensive drugs (methyldopa),



*no discrimination of acetaminophen and non-acetaminophen toxicity

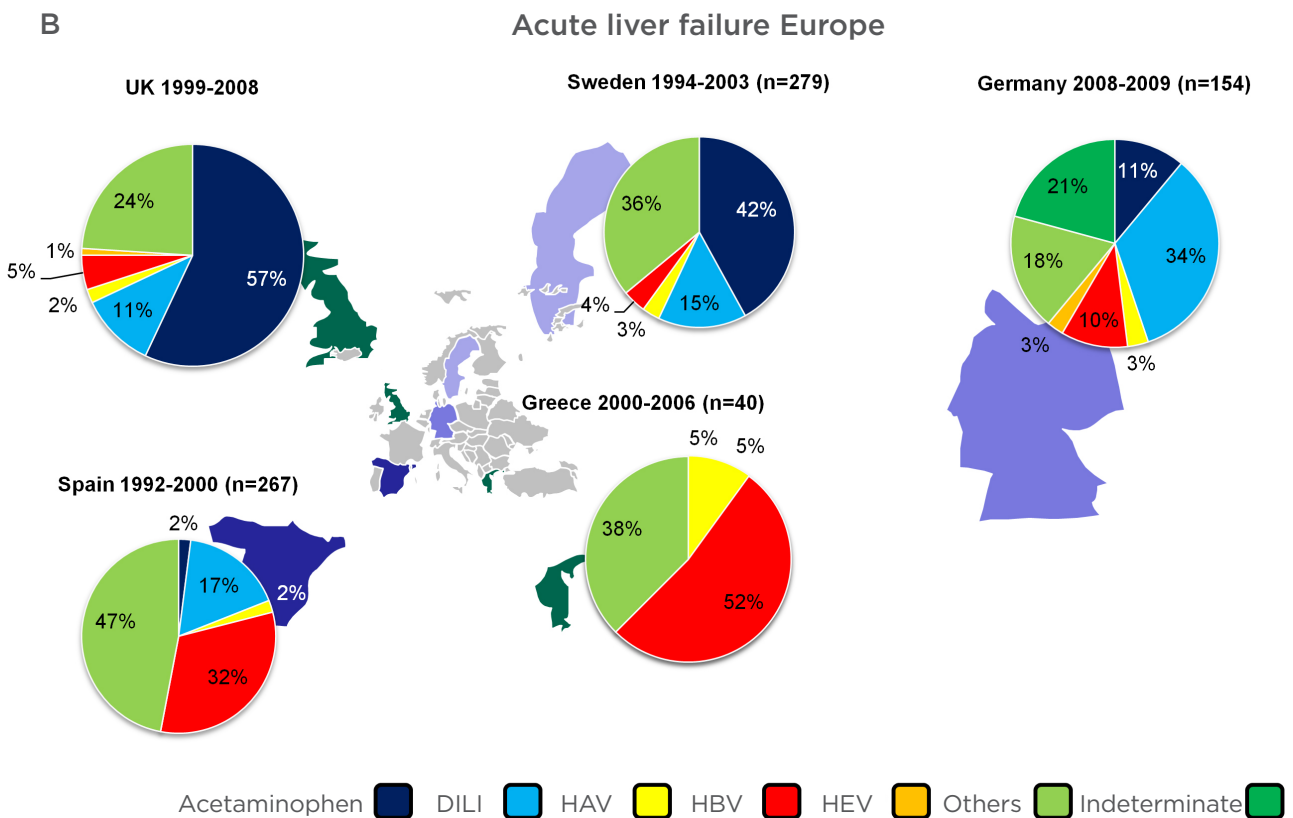


Figure 2: Distribution of main aetiologies for acute liver failure (ALF).

A) Worldwide overview of data on aetiologies for ALF.

B) Overview of European countries with studies on aetiology distribution for ALF.

Table 1: Aetiologies of acute liver failure (ALF).

Intoxication	Direct, idiosyncratic, paracetamol, ecstasy, amanita, phenprocoumon, tetracycline, halothane, isoniazid, anabolic drugs
Viral hepatitis	HBV, HAV, HEV, HBV+HDV, CMV, EBV, HSV
Immunological	Autoimmune, graft-versus-host disease (GVHD)
Metabolic	Wilson's disease, alpha-1 antitrypsin deficiency, haemochromatosis
Vascular	Budd-Chiari syndrome, ischaemic, veno-occlusive disease
Pregnancy-induced	HELLP syndrome, acute fatty liver in pregnancy

HBV: hepatitis B virus; HAV: hepatitis A virus; HEV: hepatitis E virus; HDV: hepatitis D virus; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HSV: herpes simplex virus.

anticonvulsants, antipsychotic drugs (valproic acid, chlorpromazine), and many others, including herbal medicine. Demonstrating the need for new algorithms and biomarkers of liver injury, Hy Zimmerman's observation - elevation of transaminase levels above three-times the upper limit of normal indicates early DILI - has been in use to assess the risk of DILI in drugs in development since the 1970s.²²

In a recent study, >70% of the patients with acetaminophen-induced ALF were associated with suicidal intents, while the remaining cases were a result of accidental over-dose.¹⁰ It is recognised that specific risk factors, such as obesity and excess alcohol consumption, increase the risk of acetaminophen-associated drug toxicity and DILI.²³⁻²⁵ Thus, for individuals with any cryptic liver disease or injury, current recommended dose ranges of acetaminophen might be too high. Acetaminophen serum concentration above 300 µg/mL, 4 hours after ingestion is a predictor for severe hepatic necrosis. With high doses of acetaminophen, the metabolite N-acetyl-p-benzoquinone imine (NAPQI) accumulates in hepatocytes and induces hepatocellular necrosis.^{21,26} In the presence of glutathione, NAPQI is rapidly metabolised to non-toxic products and excreted via the bile.²⁷ In acetaminophen intoxication, the glutathione pool is rapidly diminished, but could easily be restored by N-acetylcysteine therapy.

MOLECULAR MECHANISMS

ALF occurs as a result of acute hepatocellular injury from various aetiologies (toxic, viral or metabolic stress, or hypotension). However, regardless of the initial aetiology, ALF triggers a series of events inducing hepatocellular necrosis and apoptosis, reducing the regenerative capacity of the liver. Massive loss of hepatocytes consequently reduces the functional capacity of the liver for glucose, lipid, and protein metabolism, as well as biotransformation and the synthesis of coagulation factors. This then leads to encephalopathy, coagulopathy, hypoglycaemia, infections, and renal and multi-organ failure. In fact, even the pattern of hepatic cell death might be of clinical importance, as necrosis, apoptosis or necro-apoptosis seem to be specific for different causes and are associated with clinical outcome.^{28,29}

Apoptosis, programmed cell death, is a process in which ATP-dependent mechanisms lead to the activation of caspases that finally lead to the breakdown of the nucleus into chromatin bodies and disintegration of the cell into small vesicles, called apoptotic bodies, which can be cleared up by macrophages.³⁰ Upon massive cell injury, ATP depletion leads to necrosis with swelling of the cytoplasm, disruption of the cell membrane, imbalance of electrolyte homeostasis, and karyolysis. Necrosis leads to local inflammation, induction of cytokine expression, and migration

of inflammatory cells.³¹ However, apoptosis itself might induce mechanisms that lead to necrosis, and the ratio of apoptosis versus necrosis seems to play a role in liver injury.³⁰ This hypothesis is supported by observations that a death receptor agonist triggers massive necrosis secondary to the induction of apoptosis.³² It has also been shown that this severe liver injury is paralleled by fibrosis and the activation of hepatic stellate cells, even in patients without prior liver damage.³³ This type of liver fibrosis in ALF might be part of the regenerative response ('regenerative fibrosis').

The rates of apoptosis or necrosis in ongoing ALF processes seem to be different according to the underlying aetiologies.^{26,34} Apoptosis seems to be the predominant type of cell death in HBV and amanita-related ALF versus necrosis in acetaminophen and congestive heart failure.³⁵ Furthermore, antiviral treatment of fulminant HBV significantly reduced serum cell death markers and improved clinical outcome.³⁶

The regenerative capacity of the liver depends on the patient's gender, age, weight, and previous history of liver diseases. Important mediators of liver regeneration include cytokines, growth factors, and metabolic pathways for energy supply. In the adult liver, most hepatocytes are in the G₀ phase of the cell cycle and non-proliferating. Upon stimulation with the proinflammatory cytokines tumour necrosis factor α (TNF α) and interleukin-6 (IL-6), growth factors like transforming-growth factor α (TGF α), epidermal growth factor (EGF), and hepatocyte growth factor (HGF) are able to induce hepatocyte proliferation. TNF and IL-6 also induce downstream pathways related to NF κ B and STAT3 signalling. Both transcription factors are crucial for coordination of the inflammatory response to liver injury and hepatocyte proliferation.³⁷ Emerging data support an important role for hepatic progenitor and oval cells, as well as vascular endothelial growth factor (VEGF)-mediated angiogenesis in liver regeneration.³⁸⁻⁴⁰

CLINICAL PRESENTATION

Renal failure, hepatic encephalopathy, and brain oedema are the consequences of the pathophysiologic changes in ALF. Hyperammonaemia correlates with brain oedema and survival.⁴¹ Decreased hepatic urea synthesis, renal insufficiency, the catabolic state of

the musculoskeletal system, and an impaired blood-brain barrier all lead to ammonia accumulation and alterations in local perfusion, which result in brain oedema. After acute and massive hepatic cell death, the release of proinflammatory cytokines and intracellular material results in low systemic blood pressure leading to the impairment of splanchnic circulation. Renal failure in ALF patients is common in up to 70% of patients.⁴² Reduced number and function of platelets as well as inadequate synthesis of prothrombotic factors are the causes of coagulopathy. Leukopenia and impaired synthesis of complement factors in ALF patients increase the risk of infections, which might result in sepsis. Infections increase the duration of intensive care unit (ICU) stays and the mortality rate in ALF dramatically. With the impairment of hepatic gluconeogenesis, hypoglycaemia is also a frequent feature of patients with ALF.⁴³ For a more detailed discussion of the clinical presentation in ALF, the reader is referred to the recent, excellent overview by Bernal and Wendon.⁴⁴

PROGNOSIS

Accurate prediction of the clinical course is crucial for management and decision-making in ALF. Identification of the underlying aetiology improves prognosis and opens the pathway for specific treatment. The degree of hepatic encephalopathy is considered an important indicator of prognosis.¹ Cerebral oedema and renal failure worsen the prognosis dramatically. In some studies, the INR was determined as the strongest single parameter in predicting the outcome of ALF. Another interesting point is that the presence of hepatic encephalopathy implies a poor prognosis for acetaminophen-induced ALF, which, in contrast, has little meaning for amanita mushroom poisoning. LTx is the last therapeutic option in patients with ALF, when conservative treatment fails and a lethal outcome is imminent. Therefore, individual assessment if a patient will undergo a fatal course is important for timely listing. Standardised prognosis scores based on reproducible criteria are crucial tools in times of donor organ shortage and to avoid LTx in patients that might fully recover without LTx.⁴³ An overview of currently available scores to assess the severity of ALF is given in [Table 2](#).

King's College Criteria (KCC) were established in the 1990s based on findings from a cohort of

Table 2: Scoring systems in patients with acute liver failure for emergency liver transplant.

Scoring System		Prognostic factors
King's College Criteria (KCC) ⁴⁵	Paracetamol intoxication	Arterial pH <7.3 or INR >6.5 and creatinine >300 µmol/L and hepatic encephalopathy Grade 3-4
	Non-paracetamol	INR >6.5 and hepatic encephalopathy or INR >3.5 and any of these three: bilirubin >300 µmol/L, age >40 years, unfavourable aetiology (undetermined or drug-induced)
Clichy Criteria ⁴⁸	HBV	Hepatic encephalopathy Grade 3-4 and Factor V <20% (for <30 years old); <30% (for >30 years old)
MELD ^{49,50}		$10 \times [0.957 \times \ln(\text{serum creatinine}) + 0.378 \times \ln(\text{total bilirubin}) + 1.12 \times \ln(\text{INR} + 0.643)]$
CK-18 modified MELD ²⁶		$10 \times [0.957 \times \ln(\text{serum creatinine}) + 0.378 \times \ln(\text{CK18/M65}) + 1.12 \times \ln(\text{INR} + 0.643)]$
Bilirubin-lactate-aetiology score (BILE score) ⁵¹		Bilirubin (µmol/)/100 + Lactate (mmol/L) +4 (for cryptogenic ALF, Budd-Chiari or Phenprocoumon induced) -2 (for acetaminophen-induced) +0 (for other causes)
ALFSG Index ⁵²		Coma grade, bilirubin, INR, phosphorus, log ₁₀ M30
ALFED Model ⁵³		Dynamic of variables over 3 days: HE 0-2 points; INR 0-1 point; arterial ammonia 0-2 points; serum bilirubin 0-1 point

Adapted from Canbay et al.⁴³

INR: International Normalized Ratio; MELD: model of end stage liver disease.

588 patients with ALF.⁴⁵ The authors also introduced a classification based on the onset of encephalopathy after an initial rise in bilirubin levels into hyperacute (<7 days), acute (8-28 days), and sub-acute (5-12 weeks) liver failure.⁴⁶ KCC includes assessment of encephalopathy, coagulopathy (INR), acid homeostasis (pH), bilirubin, and age. For patients with acetaminophen-induced ALF, a separate KCC formula was suggested. A recent meta-analysis of 17 studies for the performance of KCC in predicting outcome in non paracetamol-induced ALF revealed a good specificity with more limited sensitivity. Moreover, the best performance of KCC was reached in groups with high grades of encephalopathy and in earlier studies.⁴⁷ Clichy criteria were introduced for patients with fulminant HBV infection and include the degree of encephalopathy and Factor V fraction as a measure for hepatic synthesis.⁴⁸

The model for end-stage liver disease (MELD) was designed to predict the likelihood of survival

after transjugular intrahepatic portacaval shunt (TIPS) in cirrhotic patients. However, it has been established for some time as an allocation tool for LTx in patients with cirrhosis in the US and Europe. The MELD has been tested for prediction of ALF and was found superior to KCC and Clichy criteria in independent studies.^{49,50} All three models are still in use but are based on clinical and laboratory data, while new options for diagnosis (molecular laboratory diagnostics) have been developed.

Novel approaches that include mechanistic characteristics of ALF, like the CK-18 modified MELD, which includes markers for hepatocellular death or lactate, are promising, but need validation in larger prospective cohorts.^{26,51,52} In a recent, large, prospective study, a prognostic model was developed using dynamic changes of four independent variables (atrial ammonia, INR, serum bilirubin, hepatic encephalopathy) over 3 days to predict mortality.⁵³ Still, the possibilities

of novel markers and diagnostic methods should be tapped to their potential to provide more accurate and reliable prognosis. A major limitation for this type of study is the relative rarity of ALF, further complicated by a variety of different regionally predominant aetiologies. To generate a reliable, widely applicable scoring system, it would be essential to establish large transnational cohorts to produce more powerful studies.

LIVER TRANSPLANT IN ALF

Recent data from the European Liver Transplant Registry (ELTR) showed that ALF accounted for 8% of indications for LTx in Europe during 1988-2009, and the survival rates after LTx have improved significantly.⁵⁴ The study by Germani et al.⁵⁴ showed 1, 5, and 10-year patient survival rates of 74%, 68%, and 63%, respectively. The 1, 5, and 10-year graft survival rates were 63%, 57%, and 50%, respectively. Similar results were observed in a US database. The authors concluded that these improvements are due to optimised pre, peri, and post-operative treatment. Another important finding of this study was the identification of combined recipient and donor age as major risk factors for early mortality after

LTx. Graft recipients older than 50 years, paired with donors older than 60 years, had a very high mortality/graft loss within the first year.⁵⁴ This suggests that better allocation algorithms for organs are needed, taking current knowledge into account.

SUMMARY

ALF continues to pose a challenge to clinicians. The identification of the underlying cause of disease remains a critical first step to allow conservative treatment, if available. Many diagnostic tools are available to help in this process, though for some patients the causes remain undetermined. As a second step, disease severity and progression will need to be evaluated to determine if LTx is necessary, and if so, the speed of organ allocation. Several scores assist this decision, though all have limitations and especially lack a positive prognostic value for patients, who can survive without LTx. Further insight into the mechanisms of individual aetiologies will probably enhance management of ALF and hopefully lead to more patients surviving without the need for transplant organs.

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