EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Prognosis indicator in acute liver failure: Is there a place for cell death markers?

Didier Samuel*, Philippe Ichai

Inserm, Unité 785, Villejuif F-94800, France; Univ Paris-Sud, UMR-S 785, Villejuif F-94800, France; AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif, France

See Article, pages 639–647

Acute liver failure (ALF) is an intriguing disease. The mechanisms by which liver cells are destroyed in just a matter of a few days, as well as the mechanisms by which the liver can regenerate itself in a few hours or days, remain partly unknown. It is unclear why some patients with the same apparent degree of severity and the same aetiology of liver failure have different outcomes. Indeed after the occurrence of encephalopathy, ALF patients can die without liver transplantation while others will recover either in a few hours or in a few days. Part of the complexity is due to the fact that ALF can occur through distinct pathways according to aetiologies; there is probably more than one mechanism responsible for ALF. Liver transplantation was a breakthrough in the treatment of ALF and has saved the lives of several thousands of patients who were at high risk of mortality [1]. However, the advent of emergency liver transplantation as a potential treatment for ALF has highlighted the need for prognosis indicators. Indeed, there is a need to establish the prognosis of patients with ALF who are at risk of mortality without liver transplantation, and also for those who will survive spontaneously or with medical care only. An additional difficulty is to have reliable criteria of prognosis early in the course of ALF in order to have sufficient time to obtain a liver graft. Assessment of the prognosis of ALF is essential when making decisions on the requirement for and timing of liver transplantation. If liver transplantation is performed too early, it may be performed when it is not necessary, and if it is performed too late, there is an increased risk of the condition worsening (neurological, infectious) with a poor outcome. The prognosis of ALF depends on many factors (gender, age, cause of liver failure, hepatic, clinical and biological status on admission and at the peak of deterioration, degree of hepatic encephalopathy, prothrombin time, factor V, INR, renal function, bilirubin level, arterial pH, lactate level, phosphoremia), and many new markers could be incorporated into prognostic models.

Age and aetiology both correlate with survival, although age does not consistently correlate with outcome in different studies. The outcome of ALF is significantly influenced by disease aetiology. In 315 patients studied from 1990 to 2001 by Brandsaeter et al., all listed for transplantation, spontaneous survival was highest in patients with HAV infection (43%), followed by paracetamol overdose (31%), HBV infection (8%), indeterminate origin (7%), and other drug-induced (0%) [2]. A high level spontaneous prognosis without liver transplantation in patients with paracetamol overdose, HAV infection, liver shock, and pregnancy-related ALF, was also reported in the USA with an overall short-term survival of $\geqslant$50% (68% for paracetamol overdose) [3]. In contrast, in this same study, patients with ALF due to indeterminate causes, drug-intoxication other than paracetamol, HBV infection, autoimmune hepatitis, Wilson's disease, and Budd–Chiari syndrome had a short-term transplant-free survival of less than 25%. Neurological status at admission and at the time of liver transplantation also influences survival. The grade of encephalopathy upon admission (grade 3 and 4) appeared to be a significant independent variable of poor outcome [4].

Different centres have proposed various prognostic criteria. The King's College Hospital (KCH) criteria [5,6] and Clichy–Villejuif criteria [1,7] remain the most widely used prognostic criteria for ALF worldwide. KCH criteria are different in patients with paracetamol and non-paracetamol-related disease. These include clinical and biological criteria (age, interval between onset of jaundice and encephalopathy, bilirubin, prothrombin time or INR, arterial pH, serum creatinine). The inclusion of other parameters such as arterial lactate has increased the sensitivity and specificity of this score (Table 1). The Clichy–Villejuif criteria include grade 3 and 4 hepatic encephalopathy and factor V levels <20% in patients <30-years of age or grade 3 and 4 hepatic encephalopathy, and factor V levels <30% if >30-years of age [1,7]. These criteria are widely used in Europe. Other studies have shown that KCH criteria have good clinical applicability, with little variation in sensitivity and specificity. Overall, fulfilment of KCH criteria is generally useful for predicting death but the absence of criteria does not predict survival.

The use of these selection criteria for transplantation in patients with ALF has some limitation. In fact, it is illusory to think that a single set of criteria is relevant to ALF of any cause. For these reasons a specific score according to some aetiology has been proposed: there are already different KCH criteria for paracetamol and non-paracetamol, specific prognostic factors

* Corresponding author. Address: Centre Hepato-Biliaire, Hôpital Paul Brousse, 94800 Villejuif, France. Tel.: +33 (1) 45 59 34 03; fax: +33 (1) 45 59 38 57.
E-mail address: didier.samuel@pbr.aphp.fr (D. Samuel).

Editorial

Table 1
Main criteria used as Prognosis indicators in acute liver failure. Other criteria can be found at Ref. [4].

Criteria	Poor prognostic factors affecting outcome of patients
Clichy–Villejuif [1,7]	
	Coma and confusion (encephalopathy stage 3–4) and factor V <20% if under 30 years or Coma and confusion (encephalopathy stage 3–4) and factor V <30% if over 30 years
KCH criteria [5,6]	
Non-paracetamol	INR >6.7 or any three of the following: Drug toxicity Indeterminate cause of acute liver failure Age <10 or >40 years Jaundice to coma interval >7 days Bilirubin >300 μm/L INR >3.5
Paracetamol	Lactate >3.5 Mmol/L Arterial pH <7.3, or lactate >3 mmol/L after adequate volume resuscitation or Encephalopathy grade 3 or 4 + creatinine >300 μm/L + INR >6.5
MELD score [11,12]	$10\times(0.957Ln_{Creatinine}[mg/L] + 0.378Ln_{Total\ Bilirubin}[mg/dL] + 1.12Ln_{INR} + 0.643$
CK18/M65 MELD score [13]	$10\times(0.957Ln_{Creatinine}[mg/L] + 0.378Ln_{M65}[U/\mu l] + 1.12Ln_{INR} + 0.643$

have been proposed for HAV-related ALF, *Amanita phalloides* poisoning, and autoimmune hepatitis [4]. Some other prognosis indicators have been proposed that take into account the severity of the medical condition, such as the Apache II score or mechanistic pathways, such as CD163 [4], and caspase level [8]. For most of these, the sensitivity is too low to determine outcome, but the specificity is acceptable. The aim of these scores is to identify, early in the course of the disease, with high accuracy, not only patients who will die without transplantation but also patients who will survive with medical treatment. An ideal predictive factor must have a high positive (PPV) and negative predictive value (NPV), but most of the time the PPV and NPV are low; this means that they are more applicable for predicting death rather than spontaneous survival.

The Mayo end-stage liver disease score (MELD) has initially been employed to determine the prognosis of cirrhotic patients treated by transjugular portacaval shunt (TIPS) [9]. The more recent score comprises three variables: bilirubin levels, INR, and creatinine levels. MELD is a quantitative tool with scores ranging from 5 to 40, a maximum score being indicative of the most severe stage. The popularity of this more recent score has arisen firstly from its linear correlation with a quantitative value and risk of death within 3 months and secondly because of the decision by the US health authorities in 2002 to allocate liver grafts as a function of cirrhosis severity [10]. The use of MELD score for the prognosis of ALF is a strange idea, since this score has not been implemented for patients with ALF. Despite these limitations, several authors have advocated the use of MELD to help decide if liver transplantation is needed or not and a cut-off of 30–35 has been proposed [11,12]. As stated above, the MELD score does not take into account very important prognosis factors in ALF such as the degree of encephalopathy. In a paper, in this issue, Bechmann et al. [paper reference] suggested to replace bilirubin in the MELD score by CK 18/M65 a marker of cell death [13]. CK 18 is a member of the intermediate filament family of cytoskeletal proteins. The caspase-dependent cleavage of CK18 exposes two epitopes: M30, a marker of apoptosis, and M65, an epitope exposed to fragmented CK18 variants released from dying cells; thus a marker of overall cell death. M65 and M30 were measured in the serum of patients with ALF by an ELISA assay. There was a good correlation between the M65 peak and absence of spontaneous recovery in contrast to bilirubin level. It is true that bilirubin in ALF is probably of low value in some aetiologies of ALF, particularly in hyperacute ALF [14]. For example, in Paracetamol overdose and in hyperacute ALF, the bilirubin level is not very high, in contrast to drug-induced ALF. The authors have thus implemented a MELD/CK18/M65 score, replacing bilirubin by M65 in the MELD scoring calculation, which looks promising. The idea is original and in their series the PPV, the NPV, the sensitivity, and specificity of this score at admission was 0.65, 0.914, 0.813, and 0.821, respectively. However, due to the low number of patients studied, it will be difficult to confirm the accuracy of this new score for each aetiological group of ALF. Before its implementation, this new score should be tested in independent cohorts. The interesting point of this approach is the use of markers of cell death and cell apoptosis to predict outcome. This is a new approach, which should be studied further. We should keep in mind that the mechanisms of ALF in humans are complex, aetiology-dependent, and are a balance between cell death by necrosis, cell death by apoptosis, and cell renewal. Thus we wonder if this CK 18 marker is more a marker of a mechanistic pathway of ALF than a true prognosis indicator. In any case, the KCH criteria and Clichy–Villejuif criteria, despite their limitations, will remain the reference standard for decisions regarding liver transplantation. Other criteria will have to be confirmed in independent cohorts and to be validated according to the aetiology of ALF. Markers of cell death or apoptosis are promising, but should be confirmed in further studies.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] 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;222:109–119.

[2] Brandsaeter B, Hockerstedt K, Friman S, Ericzon BG, Kirkegaard P, Isoniemi H, et al. Fulminant hepatic failure: outcome after listing for highly urgent liver transplantation-12 years experience in the nordic countries. Liver Transplant 2002;8:1055–1062.

[3] Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947–954.

[4] Ichai P, Samuel D. Etiology and prognosis of fulminant hepatitis in adults. Liver Transplant 2008;14:S67–S79.

[5] O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439–445.

[6] 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;359:558–563.

[7] Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. Semin Liver Dis 1986;6:97–106.

[8] Volkmann X, Anstaett M, Hadem J, Stiefel P, Bahr MJ, Lehner F, et al. Caspase activation is associated with spontaneous recovery from acute liver failure. Hepatology 2008;47:1624–1633.

[9] Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, Ter Borg PC. A model to predict poor survival in patients undergoing intrahepatic portosystemic shunts. Hepatology 2000;31:864–871.

[10] Wiesner RH, Edwards EB, Freeman RB, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–96.

[11] Yantorno SE, Kremers WK, Ruf AE, Trentadue JJ, Podesta LG, Villamil FG. MELD is superior to King's college and Clichy's criteria to assess prognosis in fulminant hepatic failure. Liver Transplant 2007;13:822–828.

[12] Dhiman RK, Jain S, Maheshwari U, Bhalla A, Sharma N, Ahluwalia J, et al. Early indicators of prognosis in fulminant hepatic failure: an assessment of the model for end-stage liver disease (MELD) and King's College Hospital criteria. Liver Transplant 2007;13:814–821.

[13] 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 failure. J Hepatol 2010;53:639–647.

[14] O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet 1993;342:273–275.