Acute liver failure (ALF) is defined as liver failure occurring within one month of the occurrence of jaundice. The disease has a grim prognosis, with a mortality of 65% to 85%. The management of ALF has till recently been conservative, and newer therapeutic modalities like biointerfaced liver, hepatocyte transplant, and extracorporeal liver assist devices have not yet been proven to be successful. Liver transplant has changed the gloomy outlook of the disease, and post-transplant survival rates of 60%–70% have been reported from most centers. However liver transplant is expensive, necessitates lifelong immunosuppression, and is limited by a global shortage of available organs. It is thus necessary to select patients who are at greatest risk of death for liver transplantation. Prognostic criteria are based primarily either on clinical and laboratory (coagulation tests, serum bilirubin) parameters, or on other parameters like liver volume. Prognostic criteria have been developed both from the East and the West; these are essentially similar except that the Western criteria take into account etiology (drug overdose being the main cause of ALF there) as well as jaundice-encephalopathy interval as factors for prognosis. The King's College criteria were one of the first prognostic systems; it has two parts for both paracetamol as well as non paracetamol ALF. The criteria from our institute found prothrombin time >25 s, serum bilirubin >15 mg/dL, age >40 years, and cerebral edema to be bad prognostic markers. Criteria from the PGIER, Chandigarh found age >50 years, raised intracranial pressure, prothrombin time >100 s, and onset of HE more than seven days after the jaundice as poor prognostic markers. All these clinical criteria have similar sensitivity and specificity. [Indian J Gastroenterol 2003;22(Suppl 2):S65-S68]

**Key words:** Drug-induced hepatitis, fulminant hepatic failure, viral hepatitis

Despite major advances in hepatology over the last two decades, acute liver failure (ALF) remains a major challenge due to its high mortality and lack of therapeutic options. Trey and Davidson defined ALF in 1969 as "the occurrence of encephalopathy within eight weeks of the onset of acute hepatic illness in an individual, in the absence of pre-existing liver disease". Other definitions based on the duration of the disease have subsequently been used to classify liver failure as hyperacute, less than 7 days; acute, 7-28 days; and subacute, 28 days to six months.

In contrast to these observations, all patients in an Indian study presented with encephalopathy within three weeks of the onset of jaundice and four weeks of the onset of other symptoms. To resolve the geographical differences on these issues of definition, nomenclature and subclassification, the International Association of the Study of the Liver (IASL) has provided a universal definition that defines ALF as that occurring within 4 weeks of the onset of jaundice and subacute liver failure as that occurring between 4 weeks and six months of the onset of jaundice.

ALF is predominantly due to the various hepatotropic viruses in the Eastern countries. Reports from India have identified hepatitis viruses as etiological agents in 95%-100% of patients with ALF, whereas in the developed world paracetamol overdose, drug-induced liver disease, metabolic liver disease like Wilson's disease, acute fatty liver of pregnancy, and toxins like mushroom poisoning are more common.

The survival rate of patients with ALF is around 33%. Two-thirds of deaths occur within 72 hours of hospitalization, indicating that any intervention or therapy must be instituted soon after hospitalization. Most deaths in ALF are caused either by cerebral edema or by sepsis, and all therapeutic modalities should be directed at the control of these complications. Recently, several methods of liver support have been devised, like extra-corporeal liver-assist devices, biointerfaced liver, extracorporeal whole organ perfusion, and hepatocyte transplantation. Even though these devices are promising, their efficacy is yet to be proved.

With the advent of liver transplantation, the gloomy outlook of ALF has improved considerably. Post-transplant survival rates ranging from 60% to 70% have been reported from most transplant centers. However transplantation is expensive, mandates life-long immunosuppression, and is limited by availability of donor organs. Therein lies the dilemma for the treating physician, i.e., whether to continue conservative treatment with an inherent risk of death, or to undertake liver transplantation ignoring the chance of spontaneous complete recovery? To resolve this dilemma a number of prognostic systems have been developed worldwide. These systems allow us to predict those patients who are at maximal risk of death and should therefore be
subjected to liver transplant.

Prognostic criteria for ALF have come up from both the East as well as the West, and considering the inherent differences in the disease in these two parts of the world, it is not surprising that these differ.

The Clichy criteria, one of the first such, originated in France and are based on factor V levels. Factor V levels below 20% of normal in those aged less than 30 years of age and below 30% of normal in those aged more than 30 years indicate a poor prognosis. All patients with factor V levels below 30% died.

Another set of criteria were published around the same time from the King’s College, London. These were based on retrospective analysis of 558 patients with ALF and were validated prospectively in 54 cases. In non-paracetamol induced ALF, the prognostic criteria included either a prothrombin time of >100 s or any three of the following: (i) age >10 or <40 years, (ii) etiology: non-A, non-B viral hepatitis or drug-induced hepatitis, (iii) icterus to encephalopathy interval longer than 7 days, (iv) prothrombin time more than 50 s, (v) serum bilirubin greater than 17.5 mg/dL. In patients with paracetamol-induced ALF, the prognostic factors included arterial pH less than 7.3, prothrombin time greater than 100 s, and creatinine greater than 3 mg/dL.

Pauwels et al assessed the performance of the Kings’ College and the Clichy criteria in a retrospective study in 81 non-transplanted patients with non-paracetamol induced ALF. Their results are shown in Table 1. In another study, Amend et al found lower predictive accuracy than that in the original study. The accuracy of these prognostic indices also decreases when they are applied to different populations, probably because of regional differences in etiology and peculiar native host factors.

In our study of 425 patients with ALF, we found the following factors to be related to worse prognosis on univariate analysis: age less than 40 years, higher grade of coma, smaller liver size, presence of cerebral edema, presence of sepsis, serum bilirubin more than 15 mg/dL, and prothrombin time exceeding 25 s. On multivariate logistic regression analysis, the following factors were found to be independently related to poor prognosis: (i) age more than 40 years, (ii) presence of cerebral edema at admission, (iii) serum bilirubin more than 15 mg/dL and (iv) prothrombin time longer than 25 s. If all the four factors were present, our prognostic model predicted mortality with a sensitivity of 0.92, specificity of 0.80, positive predictive value of 0.48 and negative predictive value of 0.98.

In another Indian study, among 206 patients with ALF studied at the Postgraduate Institute of Medical Education and Research, Chandigarh, factors associated with poor prognosis on univariate analysis were: (i) longer time interval between the onset of encephalopathy and onset of jaundice, (ii) higher grade of encephalopathy, (iii) raised intracranial pressure, (iv) prothrombin time prolongation, and (v) high serum bilirubin. Multivariate logistic regression analysis showed that the presence of (i) raised intracranial pressure at the time of admission, (ii) prothrombin time more than 100 s, (iii) age above 50 years and (iv) onset of encephalopathy more than 7 days after the onset of jaundice were associated with a poor prognosis.

Another prognostic model was published from China. It was based on 61 patients with ALF seen over a 13-year period. Six parameters found to be significant on univariate analysis were: (i) prothrombin time prolongation, (ii) high total serum bilirubin level, (iii) high serum alpha-fetoprotein level, (iv) serum cholesterol concentration, (v) older age and (vi) high serum creatinine. On step-wise logistic regression, three factors were found to independently predict mortality: (i) age above 43 years, (ii) total serum bilirubin more than 23 mg/dL, and (iii) prothrombin time prolongation exceeding 19 s. These criteria had sensitivity of 1.00, specificity of 0.67, positive predictive value of 0.95, negative predictive value of 1.00, and predictive accuracy of 0.95.

A study from Starzl’s group found that a liver volume of less than 1000 mL was associated with high mortality. Schmidt and Dalhoff have recently proposed that a serum phosphate level above 1.2 mmol/L at 48 to 96 hours after aminophenox is specifically and sensitively identifies a group of patients with little chance of spontaneous survival. However, this observation needs to be verified. Bernal et al have shown that an arterial lactate concentration in excess of 3.5 mmol/L early after transfer to a liver intensive care unit is a relative indication for listing for transplantation, whereas a concentration in excess of 3.0 mmol/L after adequate fluid resuscitation is an absolute indication. Addition of post-resuscitation lactate concentration to the King’s College criteria increased the latter’s sensitivity from 76% to 91% and lowered the negative likelihood ratio from 0.25 to 0.10. However, validation studies from more centers are awaited.

On comparing various clinical criteria (Table 2), one finds that age and prothrombin time prolongation have been used in all, and serum bilirubin levels have been used in three of four models. Thus, these three parameters constitute the three most-uniformly agreed-upon bad prognostic factors for patients with ALF.
### Table 2: Comparison of various clinical criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Age</th>
<th>Serum Prothrombin</th>
<th>J-HEE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(years)</td>
<td>(mg/dL)</td>
<td>time (sec)</td>
</tr>
<tr>
<td>King's College 1</td>
<td>&lt;10&lt;40</td>
<td>&gt;17.5</td>
<td>&gt;50</td>
</tr>
<tr>
<td>New Delhi 2</td>
<td>&gt;40</td>
<td>&gt;15</td>
<td>&gt;25</td>
</tr>
<tr>
<td>Chandigarh 3</td>
<td>&gt;50</td>
<td>-</td>
<td>&gt;100</td>
</tr>
<tr>
<td>China 4</td>
<td>&gt;43</td>
<td>&gt;23</td>
<td>19</td>
</tr>
</tbody>
</table>

CE = cerebral edema; J-HEE = jaundice-encephalopathy interval

### Table 3: Performance of various prognostic models

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>King's College 5</td>
<td>0.96</td>
<td>0.90</td>
<td>0.93</td>
<td>0.92</td>
<td>0.92</td>
</tr>
<tr>
<td>New Delhi 6</td>
<td>0.92</td>
<td>0.80</td>
<td>0.48</td>
<td>0.98</td>
<td>0.82</td>
</tr>
<tr>
<td>China 7</td>
<td>1.00</td>
<td>0.67</td>
<td>0.95</td>
<td>1.00</td>
<td>0.95</td>
</tr>
<tr>
<td>Cholic 8</td>
<td>0.92</td>
<td>0.85</td>
<td>0.95</td>
<td>0.90</td>
<td>0.94</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value; PA, predictive accuracy

The performance of various prognostic models is summarized in Table 3. Thus, all the prognostic models have similar sensitivity, specificity, positive predictive value, negative predictive value, as well as predictive accuracy except those developed at our center, which have a lower positive predictive value. This is possibly due to the fact that, in this cohort, only a few patients had all the four factors.

Western studies differ from Indian and Chinese reports in two major ways. First, in the West, etiology of disease is an important prognostic factor and ALF due to drugs and non-A, non-B viruses have a higher mortality as compared to that due to hepatitis A and B. Second, in the West, jaundice-encephalopathy interval was related to prognosis such that patients with more rapid development of encephalopathy had better survival; this association was found in only one Indian study. Presence of cerebral edema at admission was found to be an independent prognostic marker of poor prognosis on multivariate analysis in both Indian studies (Table 2).3,11

In conclusion, prognostic criteria are a simple and effective method to predict mortality of ALF and are helpful in deciding therapeutic strategy for these patients. Their use is likely to increase with the increasing availability of facilities for liver transplant.

### References