ORIGINAL ARTICLES—LIVER, PANCREAS, AND BILIARY TRACT

Prognostic Implications of Lactate, Bilirubin, and Etiology in German Patients With Acute Liver Failure

JOHANNES HADEM,* PENELOPE STIEFEL,* MATTHIAS J. BAHR,* HANS L. TILLMANN,‡ KINAN RIFAI,* JÜRGEN KLEMPNAUER,§ HEINER WEDEMEYER,* MICHAEL P. MANNS,* and ANDREA S. SCHNEIDER*

*Department of Gastroenterology, Hepatology and Endocrinology, and §Department of Visceral and Transplant Surgery, Hannover Medical School, Hannover; and ‡Medical Clinic and Policlinic II, University of Leipzig, Leipzig, Germany

Background & Aims: **Among the potentially helpful indicators of poor prognosis in acute liver failure (ALF) are etiology, encephalopathy grade, blood lactate, and King's College Criteria (KCC). The accuracy of these parameters in predicting transplantation or death shows significant variation in different countries.** ***Methods:*** **We retrospectively analyzed 102 patients with ALF treated at our institution between 1996 and 2005. Baseline parameters, simplified acute physiology score III (SAPS-III), KCC, Model for End-Stage Liver Disease (MELD) score, and a novel score of bilirubin, lactate, and etiology (BiLE score) were compared between transplant-free survivors and patients who required liver transplantation or died, by using multivariate linear regression analysis and receiver operating characteristics (ROC).** ***Results:*** **The most common causes of ALF were indeterminate liver failure (21%), acute hepatitis B (18%), acetaminophen ingestion (16%), and Budd-Chiari syndrome (9%). Transplantation-free survival was 38%, 44% of patients underwent liver transplantation, and 18% died without transplantation. Eight-week survival was 77%. The BiLE score was the best predictor of death or need of transplantation, with 79% sensitivity and 84% specificity. ROC analysis revealed a better performance of BiLE score when compared with bilirubin, lactate, MELD score, and SAPS-III (area under the curve: 0.87 ± 0.04, 0.73 ± 0.51, 0.73 ± 0.52, 0.71 ± 0.05, and 0.68 ± 0.59, respectively).** ***Conclusions:*** **The simple, combined BiLE score emerged as the best predictor of poor outcome in our patient cohort and should be prospectively evaluated in other populations.**

In 1970, Trey and Davidson[1] defined acute liver failure (ALF) as an acute deterioration of liver function resulting in the development of encephalopathy within 8 weeks of the onset of symptoms in a patient with a previously healthy liver. According to the recent position paper of the American Association for the Study of Liver Diseases, ALF is defined as decline in liver function of less than 26 weeks' duration, absence of cirrhosis, evidence of coagulation abnormality (usually indicated by an international normalized ratio [INR] ≥1.5), and any degree of encephalopathy. Patients with Wilson's disease, vertically acquired HBV, or autoimmune hepatitis might be included in spite of possible cirrhosis if the disease has only been recognized for less than 26 weeks.[2] The composition of etiologies varies among geographic regions, an issue that has been addressed by a number of studies.[3] King's College Hospital London reported 57% acetaminophen toxicity and 9% viral hepatitis among 1014 patients between 1973 and 1991.[4] A large prospective study involving 17 sites in the United States (Acute Liver Failure Group) collected data of 308 patients regarding etiology, clinical and laboratory features, and outcome of patients presenting with ALF. The most common etiologies were acetaminophen overdose (39%), indeterminate (17%), idiosyncratic drug reactions (13%), and viral hepatitis A and B (12%).[5] Early reports from France indicated viral hepatitis to be the most important cause of ALF in central Europe,[6] with acute hepatitis B accounting for up to 45% of cases.[7] The diversity of etiologies was just recently assessed by an international survey of 6 liver transplantation centers summarizing 284 ALF cases. Although acetaminophen was the dominant etiology in London and Copenhagen with 55% and 74% of cases, respectively, hepatitis B (including acute exacerbations of chronic hepatitis B) was the most prominent etiology in Hong Kong (74%) and Karachi (38%). In addition, a high proportion of cases in Karachi (35%) were due to hepatitis E.[8]

A major problem in the management of ALF is the prediction of spontaneous recovery. Of numerous proposed prognostic criteria for ALF, the King's College criteria (KCC) have been the most commonly used and most frequently evaluated.[9] KCC are probably the best validated tool currently available.[10] However, the predictive value of KCC in the U.S. has been questioned[11] and has not been sufficiently evaluated in central Europe, where acetaminophen is not the leading cause of ALF.[12] Depending on etiology, KCC were shown to have a positive predictive value of 79%–88% and negative predictive value of

Abbreviations used in this paper: ALF, acute liver failure; AUC, area under the curve; BiLE, bilirubin-lactate etiology; ICU, intensive care unit; INR, international normalized ratio; KCC, King's College Criteria; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; ROC, receiver operating characteristics; SAPS-III, simplified acute physiology score III.

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50%–65%.[13] In France, Clichy criteria are widely used to select ALF patients in need of orthotopic liver transplantation (OLT). Besides the presence of hepatic encephalopathy, they include patients' age and factor V levels.[14] Only a few studies have attempted to directly compare the Clichy criteria and KCC, suggesting superiority of the KCC.[15,16] In acetaminophen-induced ALF, blood lactate levels above 3.0 mmol/L had a sensitivity of 76% and specificity of 97% in predicting death,[17] but results diverged in non–acetaminophen-related ALF.[18–22] According to the large prospective U.S. multi-center study, encephalopathy grade at admission and etiology were the only predictors of outcome.[5] Recently, Yantorno et al[23] have suggested a cut-off value above 30 of the Model for End-Stage Liver Disease (MELD) score as predictor of poor outcome. The objectives of our retrospective analysis were to evaluate these prognostic parameters in a central European cohort.

Methods

Patients and Clinical Assessment

We retrospectively identified 210 patients with acute hepatic dysfunction treated at the intensive care unit of our institution between 1996 and 2005. Of those, 102 patients (Figure 1) fulfilled the diagnostic criteria of ALF as initially published by Trey and Davidson[1] as well as those recently defined by the American Association for the Study of Liver Diseases (ie, hepatic encephalopathy, acute-onset increase of INR >1.5, and absence of signs of chronic liver disease in clinical and ultrasound examination).[2]

The study was approved by the human research committee of the Medical School Hannover, thereby confirming that the protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent for retrospective data acquisition was obtained from all patients whose current postal address was available or from patients' next of kin in case of a fatal outcome.

All parameters except the maximum encephalopathy grade were documented at admission to intensive care unit (ICU). Outcome end points included liver transplantation, death, and survival without transplantation for at least 8 weeks after admission at ICU. Hepatic encephalopathy was graded on a standard scale of I–IV as described previously.[24] Simplified acute physiology score (SAPS) III, which is currently being evaluated as a predictive model in critical care patients, was calculated by using an EXCEL (Microsoft Corp, Redmond, WA) file provided by the SAPS-III Outcomes Research Group (www.saps3.org). KCC were determined as described.[9] The calculation of MELD score was performed according to the equation: MELD score = [9.57 × $\log_e$ creatinine (mg/dL) + 3.78 × $\log_e$ bilirubin (mg/dL) + 11.20 × $\log_e$ INR + 6.43].[25] In addition to the established predictive tools, we introduced a simple combined bilirubin-lactate-etiology score (or BiLE score) that can be calculated right at the beginning of the ICU stay. The calculation of BiLE score, which was developed empirically, is BiLE score = (baseline bilirubin [μmol/L]/100) + baseline lactate [mmol/L] + 4 [in case of indeterminate ALF, Budd-Chiari syndrome, or phenprocoumon toxicity] − 2 [in case of acetaminophen toxicity] + 0 [in case of any other ALF etiology] (Table 1). These parameters were then compared between the cohort of transplant-free survivors and patients who needed liver transplantation or died.

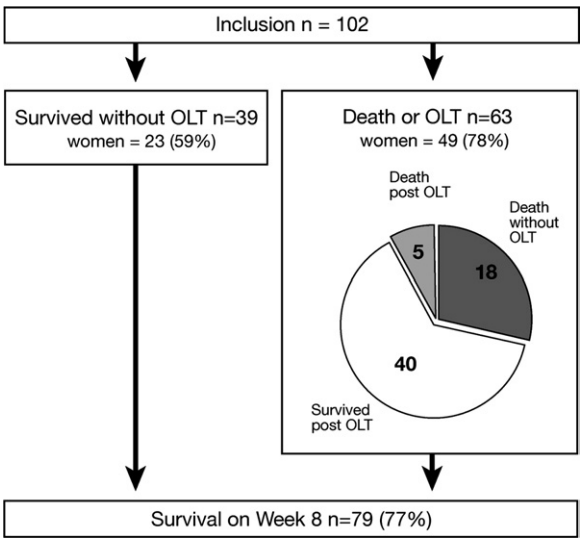

Figure 1. Outcome of 102 patients included in the retrospective analysis.

Table 1. BiLE Score

BiLE score
Bilirubin (μmol/L)/100 + lactate (mmol/L)
+4 (in case of indeterminate ALF, Budd-Chiari syndrome, or phenprocoumon toxicity)
−2 (in case of acetaminophen toxicity)
+0 (in case of any other ALF etiology)

NOTE. Sensitivity and specificity in predicting liver transplantation or death were calculated by using a BiLE score cut-off value >6.9.

Diagnoses were based on accepted diagnostic criteria that involved history, laboratory values, ultrasound imaging, and in individual cases histopathologic examination. Indeterminate ALF was assumed when the above mentioned diagnostic procedures including toxicology screens and serology for hepatitis A, B, and C, herpes simplex virus, varicella zoster virus, cytomegalovirus, and Epstein-Barr virus as well as autoantibodies were inconclusive. Decision to enroll a patient in the high urgency liver transplantation program was made according to the guidelines of the Eurotransplant International Foundation (see www.eurotransplant.nl for details).

Statistical Analysis

All calculations were performed with SPSS software (version 13.0; SPSS Inc, Chicago, IL). Results are expressed as medians and ranges unless otherwise stated. Differences in discrete variables were tested with the χ^2 test or the Fisher exact test, wherever appropriate. Continuous variables were compared with the *t* test for normally distributed variables and with the Mann-Whitney test for non-normally distributed variables. Multivariate linear regression analysis was performed to evaluate prognostic value. Receiver operating characteristic (ROC) curves were calculated for the most relevant parameters.

Results

Demographic Characteristics and Clinical Data

Of the 102 patients with acute liver failure, 72 (71%) were women. The median age of the group was 38 years (range,