A Model for Predicting Development of Overt Hepatic Encephalopathy in Patients With Cirrhosis

Q30 Oliviero Riggio,[*] Piero Amodio,[‡] Alessio Farcomeni,[§] Manuela Merli,[*] Silvia Nardelli,[*] Chiara Pasquale,[*] Ilaria Pentassuglio,[*] Stefania Gioia,[*] Eugenia Onori,[*] Nicole Piazza,[*] Michele De Rui,[‡] Sami Schiff,[‡] and Sara Montagnese[‡]

[*]Department of Clinical Medicine, Center for the Diagnosis and Treatment of Portal Hypertension, [§]Department of Public Health and Infectious Diseases, "Sapienza" University of Rome, Rome, Italy; [‡]Department of Medicine, University of Padua, Padua, Italy

Q6 **BACKGROUND & AIMS:** **Overt hepatic encephalopathy (HE) affects patients' quantity and quality of life and places a burden on families. There is evidence that overt HE might be prevented pharmacologically, but prophylaxis would be justified and cost effective only for patients at risk. We aimed to identify patients with cirrhosis at risk for overt HE.**

METHODS: **We collected data from October 2009 through December 2012 for 216 consecutive patients with cirrhosis (based on liver biopsy, 96 patients with minimal HE), admitted to the Gastroenterology Unit at the University of Rome. Patients were followed up and evaluated for an average of 14.7 ± 11.6 months; development of overt HE was recorded. We analyzed end-stage liver disease scores, shunt placement, previous overt or minimal HE, psychometric hepatic encephalopathy score (PHES), and levels of albumin, bilirubin, creatinine, and sodium to develop a prediction model. We validated the model in 112 patients with cirrhosis seen at the University of Padua and followed up for 12 ± 9.5 months.**

RESULTS: **During the follow-up period, 68 patients (32%) developed at least 1 episode of overt HE. Based on multivariate analysis, the development of overt HE was associated with previous HE, minimal HE (based on PHES), and level of albumin less than 3.5 g/dL (area under the curve [AUC], 0.74). A model that excluded minimal HE but included albumin level and previous HE also identified patients who would develop overt HE (AUC, 0.71); this difference in AUC values was not statistically significant ($P = .104$). Both models were validated in the independent group of patients (3 variables: AUC, 0.74; 95% confidence interval, 0.66–0.83; and 2 variables: AUC, 0.71; 95% confidence interval, 0.63–0.78).**

Q7

CONCLUSIONS: **We developed and validated a model to identify patients with cirrhosis at risk for overt HE based on previous HE, albumin levels, and PHES. If PHES was not available, previous HE and albumin levels still can identify patients at risk. Psychometric evaluation is essential for patients with no history of HE. These findings should aid in planning studies of pharmacologic prevention of overt HE.**

Keywords: Liver Disease Progression; Risk Analysis; Mental Health; Fibrosis.

Q8 Q9 Q10 Q11 Overt hepatic encephalopathy (HE) is a major complication of cirrhosis[1] with a negative impact on survival.[2–4] Prospective studies have shown that even a single episode of overt HE is accompanied by the acquisition of defects in learning capacity, reaction time, and working memory,[5,6] supporting the observation that cognitive impairment is more frequent and severe in patients with a history of overt HE. Thus, overt HE seriously affects both the quantity[3] and the quality of the patient's life.[7] In addition, it represents a burden for the patient's families[8] and can cause a reduction in working activity and financial income for the affected patients.[9] For all of these reasons, measures for the prevention of overt HE are probably worthy of adoption and it would be important to identify cirrhotic patients who are at risk of HE.

Abbreviations used in this paper: **AUC, area under the receiver operator characteristic curve; HE, hepatic encephalopathy; NRI, Net Reclassification Index; PHES, Psychometric Hepatic Encephalopathy Score; ROC, receiver operator characteristic; TIPS, transjugular intrahepatic portosystemic shunt.**

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.12.025

To this aim, in this prospective observational study, a number of clinical and laboratory variables were recorded and related to the development of overt HE during the follow-up period. The prognostic model derived from the observation group enrolled in Rome was tested in an independent validation group of patients observed and followed up in Padua.

Patients and Methods

From October 2009 to December 2012, all consecutive cirrhotic patients without overt HE admitted to the Gastroenterology Unit in Rome were enrolled. The diagnosis of cirrhosis was based on liver biopsy or on clinical, biochemical, and ultrasonographic findings. An upper endoscopy always was performed at the time of inclusion to evaluate the size of esophageal varices. Overt HE was excluded based on the West–Haven criteria.[10] Exclusion criteria were as follows: alcohol/psychoactive drug intake at baseline, neurologic disease, and lack of compliance with psychometric evaluation. Patients with advanced hepatocellular carcinoma, outside the Milan criteria, also were excluded. Patients with a history of persistent or recurrent HE defined by 2 or more episodes within the past 6 months, even without overt HE on first observation, also were excluded because these patients usually are treated continuously with lactulose and/or nonabsorbable antibiotics and because in these patients the occurrence of overt HE is expected by definition.

Informed, written consent was obtained. The "Sapienza" University of Rome Ethical Committee approved the study (Rif.1720/01.10.09).

A detailed history was obtained regarding previous episodes of overt HE. Patients were qualified as having a positive history if a previous episode of overt HE (grade II or higher based on the West Haven criteria) was documented by a hospitalization. The cut-off value for grade II HE was the presence of an acute confusional syndrome with disorientation to time on neurologic examination. If the patient or a family member reported a less severe degree of HE (grade I, covert HE) the patient was qualified as having a negative history of overt HE. All of the other parameters (Child–Pugh class and score, model for end-stage liver disease score, serum sodium level, and albumin level) were collected at enrollment. Portal-systemic shunts (splenorenal or mesenteric-caval shunts) were searched for by ultrasound and computed tomography scan in all patients. In patients who received a transjugular intrahepatic portosystemic shunt (TIPS), the shunt patency was checked by ultrasound examination.

Psychometric Evaluation

All patients underwent the psychometric hepatic encephalopathy score (PHES) battery, including the digit-symbol test, trail-making test A and B, the serial-dotting test and the line-tracing test. Each test was scored against age- and education-adjusted norms for the Italian population. The PHES is the sum of the integer scores of each test computed from the adjusted Z values, as follows: score of -3 for $Z \leq -3$; score of -2 for $-3 < Z \leq -2$; score of -1 for $-2 < Z \leq -1$; score of 0 for $-1 < Z < 1$; and score of 1 for $Z \geq 1$. A PHES of -4 or less was considered abnormal.[11]

Follow-Up Evaluation

All patients were followed up with repeated ultrasound and laboratory investigations every 6 months and an endoscopic evaluation every year. Patients and their families were instructed to contact physicians immediately should any alteration in mental status occur between scheduled reviews. Patients' families were instructed to report the occurrence of lethargy, apathy, personality change, inappropriate behavior, or disorientation in time and place. If this occurred, HE psychometric evaluation was repeated. Patients with an overt episode of HE reached the main end point of the study. The patients were contacted by telephone every 3 months to check on their adherence to the scheduled follow-up evaluation.

None of the patients received any pharmacologic treatment to prevent the occurrence of HE. Once developed, HE was treated with oral administration of nonabsorbable disaccharides or antibiotics. All potential HE precipitating events also were treated. The patients were followed up until death, liver transplantation, or to the last available outpatient review.

Validation Study

The database of all the patients observed and followed up in the Department of Medicine (University of Padua) was used. Patients were selected if the data included in the model for HE prediction development by the observation group were available at entry. The development of an episode of overt HE (grade II or higher) recorded during the follow-up period was the end point for the validation group as well.

Statistical Analysis

Comparisons among groups were performed by analysis of variance, an unpaired Student *t* test, or the chi-square test. The cumulative incidence of the first episode of HE during the follow-up evaluation was estimated. The conditional hazard at multivariate analysis, owing to the competing risk nature of the data (HE and death), was evaluated using the proportional subdistribution hazards model of Fine and Gray.[12] We therefore report the subdistribution hazard ratios rather than the usual hazard ratio, however, the former has the same interpretation as the latter.