Factors That Predict 1-Month Mortality in Patients With Pregnancy-Specific Liver Disease

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BACKGROUND & AIMS: **Pregnancy-specific liver diseases such as acute fatty liver of pregnancy; hemolysis, elevated liver enzymes and low platelet syndrome; and preeclampsia-associated liver disease are associated with considerable morbidity and mortality. We investigated the ability of the model for end-stage liver disease (MELD) to predict 1-month mortality among patients with pregnancy-specific liver diseases. We also developed and tested a model to predict mortality based on features of pregnancy-specific liver diseases.**

METHODS: **We performed a retrospective study, analyzing hospital admission, clinical, hematologic, and biochemical data collected from 130 patients with pregnancy-specific liver diseases admitted to the St. John's Medical College Hospital (Bangalore, India) from January 2000 through April 2011. Patients were followed up until 3 months after delivery or death. Logistic regression models were fitted using the MELD score and other variables identified as clinically or statistically significant. The predictive accuracy and calibration of the models were assessed by receiver operating characteristic curves and the Hosmer–Lemeshow goodness-of-fit test.**

RESULTS: **Thirty-two patients (24.6%) died. Mortalities from pregnancy-specific liver diseases within 1 month of admission among patients with MELD scores of 20 to 29, 30 to 39, or 40 or greater were 24.2%, 45.45%, and 90.9%, respectively. Univariate analysis identified encephalopathy, ascites, serum total protein, bilirubin, platelet count, alkaline phosphatase, serum creatinine, and international normalized ratio (INR) as significant variables. Multivariate analysis identified total bilirubin ($P < .001$) and INR ($P < .003$) as significant predictors of mortality. MELD score and a model based on only 2 variables (bilirubin level and INR) accurately predicted mortality (C statistics, 0.83 and 0.86, respectively) and were well calibrated (Hosmer–Lemeshow $\chi^2 = 9.7$ [$P = .28$] and 1.9 [$P = .98$], respectively).**

CONCLUSIONS: **A new logistic model based on only 2 variables (INR and total bilirubin) was comparable with the MELD model in predicting mortality among women with pregnancy-specific liver diseases.**

Keywords: HELLP Syndrome; Prognostic Factor; Survival; Outcome.

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Pregnancy-specific liver diseases (PsLDs), which include pre-eclampsia–associated liver diseases; hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome; and acute fatty liver of pregnancy (AFLP), are associated with considerable morbidity and mortality.[1–7] In contrast, intrahepatic cholestasis of pregnancy is a distinct disease whose predominant features of pruritus and cholestasis seldom are associated with hepatic insufficiency.[1,2] There is a marked degree of overlap in the clinical and histologic features between the subsets of PsLD patients, such that they often are considered a spectrum of the same disease.[8–14] Mortality historically has been high, but has decreased considerably. More recent studies, however, have indicated that morbidity and mortality still may be substantial.[15,16] A recent report from the King's College group in London reported rates of mortality and liver transplantation that

Abbreviations used in this paper: AFLP, acute fatty liver of pregnancy; HELLP, hemolysis, elevated liver enzymes, and low platelet; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PsLD, pregnancy-specific liver disease; ROC, receiver operating characteristic.

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reached 20%.[15] Therefore, early recognition and prompt transfer to advanced centers and delivery are critical to improve survival in PsLD.

Although features such as thrombocytopenia, renal failure, ascites, encephalopathy, and coagulopathy[17–19] signify severe disease, these features seldom occur in isolation.[9–11] Given the considerable overlap in the clinical and laboratory characteristics among the subsets of PsLD and also given the considerable morbidity, there is a critical need to identify factors associated with poor outcome; this would enable the treating physician to identify those who survive with supportive measures and those who require advanced care and transfer or referral for liver transplantation. Little has been published about the predictors of survival in PsLD. Moreover, because of the multisystemic nature of the disease, input from physicians across different specialties often is obtained in assessing the severity of disease, the timing of intervention (delivery), and management and transfer to advanced centers.[19,20]

Although disease-specific prognostic criteria are available for some diseases, prognostic scoring systems have not been evaluated systematically in PsLD. The most popular and the most widely used of the acute liver disease prognostic models is the Kings College criteria, which recently were evaluated by the Kings College group.[15] The investigators found the model not effective in predicting outcome.[15] Another model, the Model for End-stage Liver Disease (MELD),[21] has been investigated and validated as an important stratification tool in patients with acute disease such as acute liver failure and alcoholic liver disease.[22–25] However, MELD has not been evaluated in predicting outcome in PsLD, a cohort greatly different from all other disease cohorts. In addition, the role of pregnancy-specific variables such as maternal and gestational age in influencing the outcome in PsLD is not clear. Therefore, we aimed to determine the predictors of severity in PsLD and investigated the ability of the MELD to predict 1-month mortality among patients with PsLD. We also developed and tested a new model to predict mortality based on features of PsLD.

Patients and Methods

We performed a retrospective study of consecutive pregnant patients with liver disease or jaundice from January 2000 to April 2011, admitted to the St. John's Medical College Hospital in Bangalore (India), which is a university teaching hospital with access to primary and tertiary referral care. Patients were identified from the registry of patients with PsLD maintained by the department. The diagnosis and management of patients with PsLD and its subgroups recently was reported.[9] The diagnosis of AFLP, HELLP, and pre-eclampsia–associated liver diseases were based on standard criteria.[3,4,6,9] Briefly, the diagnosis of HELLP was based on the presence of thrombocytopenia (platelet count $<100{,}000/mm^3$) in the presence of jaundice and liver biochemical test abnormalities and hemolysis, whereas AFLP was based on the presence of increased uric acid levels, increased prothrombin time, hypoglycemia, and liver test abnormalities. Given the overlapping clinical and laboratory characteristics, all such patients were analyzed together under the collective term *pregnancy-specific liver disease*.[9,10,19] Competing causes such as acute viral hepatitis A through E and intrahepatic cholestasis of pregnancy were excluded. Other causes of jaundice and/or thrombocytopenia caused by malaria, leptospira, dengue, and herpes simplex virus also were excluded. This study was approved by the St. Johns Medical College and Research Institution ethical review board.

Patients underwent a detailed clinical, hematologic, biochemical, and ultrasonography assessment of the abdomen and pelvis on admission. Details regarding delivery of the patients recently were described.[9] All patients were delivered before death. Patients were followed up until 3 months after delivery or death.

We analyzed the admission variables and selected for analysis those clinical and laboratory variables that have an effect on pregnancy per se (maternal age, gestational age, primiparous, and hypertension) and the variables that are an indicator of liver disease (ascites, encephalopathy, total protein level, serum albumin level, total bilirubin level, direct bilirubin level, aspartate aminotransferase level, alanine aminotransferase level, alkaline phosphatase level, international normalized ratio [INR], platelet count, serum creatinine level, hemoglobin level, white cell count, serum sodium level, serum potassium level, and serum glucose level). The MELD score was calculated using the original MELD formula using admission characteristics as shown: $(9.57 \log [\text{creatinine}] + 3.78 \log [\text{bilirubin}] + 11.20 \log [\text{INR}] + 6.43)$.[21]

Statistical Analysis

Continuous variables were tested for normal distribution and were expressed as means $\pm$ standard deviations, whereas noncontinuous variables were presented as medians and ranges. Bivariate analysis was performed, with death as the outcome of interest. Continuous variables were assessed with t tests, and variables that were not distributed normally were assessed by the Wilcoxon rank-sum test. Categoric variables were assessed using the chi-square test.

Univariate logistic regression analysis was performed and covariates with a P value of .1 or less were considered significant (to avoid eliminating significant variables). The variables found to be significant in the univariate analysis and the variables that were clinically significant were included in the multivariate analysis.

Logistic regression was used for model development with MELD variables, and with the variables identified as significant in the univariate analysis. All analyses were