Prevalence and Predictors of Esophageal Varices in Patients With Primary Biliary Cirrhosis

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Background & Aims: **Esophageal varices and bleeding are among the most feared complications of primary biliary cirrhosis (PBC). We aimed to determine the prevalence of esophageal varices in patients with PBC, to evaluate noninvasive markers of esophageal varices in this population, and to validate the results in an independent set of patients.** ***Methods:*** **Data were collected on all patients with PBC seen for the first time at the University of Florida (study group) and at Case Western Reserve University hospitals (cross-validation group) during 7 consecutive years. Logistic regression analysis was used to identify independent predictors of esophageal varices. The best cut-off values were calculated based on receiver operating characteristic curves. The diagnostic accuracy of the independent predictors of esophageal varices identified in the study group were retested in the cross-validation group.** ***Results:*** **Of 210 patients with PBC seen at the University of Florida, 113 had an endoscopy and 49.6% (56 of 113) were found to have esophageal varices. After excluding 22 patients with a history of variceal bleeding, data on 91 patients were analyzed. Thirty-four patients had esophageal varices (37%). Multivariate analysis revealed that a platelet count of less than 140,000 (odds ratio, 7.6; 95% confidence interval, 1.6–37) and a Mayo risk score of 4.5 or greater (odds ratio, 10.6; 95% confidence interval, 1.8–62) were independent predictors of esophageal varices. The diagnostic accuracy of these predictors was confirmed in an independent set of patients.** ***Conclusions:*** **Among patients with PBC, a platelet count of less than 140,000 and/or a Mayo risk score of 4.5 or greater appears to identify those patients more likely to benefit from a screening endoscopy.**

Variceal bleeding is among the most serious complications of portal hypertension. Esophageal varices are present in roughly 50% of all cirrhotic patients, with a 2%–15% annual incidence of bleeding.[1] Despite recent advances in medical management, the probability of death after the first episode of bleeding remains 15%–21%.[2–4] Such high mortality combined with the efficacy of primary prophylaxis, which leads to a 40% reduction in the risk of death, reinforce the need for a systematic approach to detect varices in at-risk patients.[5,6] Practice guidelines endorsed by the American Association for the Study of Liver Diseases in 1998 suggest that all newly diagnosed cirrhotic patients should be screened for esophageal varices; those with large varices should be treated with β-blockers, and those with small varices should be rescreened in approximately 1 year.[6] These recommendations, however, may not apply to patients with primary biliary cirrhosis (PBC), who may develop portal hypertension without frank cirrhosis.

PBC is a chronic cholestatic liver disease characterized by progressive destruction of interlobular bile ducts and chronic cholestasis, eventually leading to cirrhosis and its complications.[7] Approximately one third of patients with PBC develop esophageal varices during follow-up evaluation, and half of these will have a documented episode of variceal bleeding.[8,9] More recent studies, however, have indicated a lower prevalence of varices (8%–19%), perhaps owing to the long-term use of ursodeoxycholic acid (UDCA).[10–12] Despite a strong correlation between advanced stages of PBC and the presence of esophageal varices, portal hypertension can occur during early stages of the disease. In addition to sampling error, several explanations exist for this occurrence, including significant portal tract inflammation causing portal venous compression, perisinusoidal fibrosis, and nodular regenerative hyperplasia.[13–16] Thus, in this population, complications of portal hypertension can occur before the development of cirrhosis. Further complicating the matter, a liver biopsy examination is not always necessary to make a diagnosis of PBC,[17] nor is it included in the most commonly used prognostic index for this disease, the Mayo risk score.[18] Therefore, many experts are moving away from performing diagnostic and follow-up liver biopsy procedures in PBC, which reduces the likelihood of diagnosing cirrhosis.

Although several groups have attempted to define noninvasive predictors of esophageal varices among cirrhotic patients,[19–27] a consistent and reproducible marker has not been identified for use in clinical practice.[28] In addition, patients with PBC were largely underrepresented in these studies. Angulo et al[10] evaluated data from 180 PBC patients who participated in a clinical trial, of whom 138 had screening esophagogastroduodenoscopy (EGD). The only noninvasive independent predictor of varices was the Mayo risk score. Ninety-three percent of patients who developed varices had a Mayo risk score of 4 or greater. More recently, Bressler et al examined a subgroup of 86 patients with PBC (n = 79) or primary sclerosing cholangitis (n = 7) who underwent EGD and found that a platelet count of less than 200,000/mm^3, an albumin level of less than 4.0 g/dL, and a bilirubin level greater than 20 μmol/L (1.16 mg/dL) were independent predictors of

Abbreviations used in this paper: AMA, antimitochondrial antibody; EGD, esophagogastroduodenoscopy; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

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Table 1. Characteristics of 127 Patients With PBC Without Previous Variceal Bleeding

Characteristics	Study group (n = 91)	Cross-validation group (n = 36)	*P* value
Females	84 (92%)	29 (81%)	.04
Age, *y*	58 ± 1.1	57.5 ± 1.9	NS
AMA titer ≥ 1:40[a]	62/86 (72.1%)	32/33 (97%)	.001
Serum alkaline phosphatase level (normal range, 35–129 *U/L*)	274 ± 25	232 ± 57	NS
Serum bilirubin level (normal range, 0.0–1.0 *mg/dL*)	0.9 ± 0.5	1.2 ± 0.5	NS
Serum aspartate aminotransferase level (normal range, 0–37 *U/mL*)	61 ± 5.8	59 ± 14	NS
Serum alanine aminotransferase level (normal range, 0–41 *U/mL*)	56 ± 7.0	58 ± 8.4	NS
Serum albumin level (normal range, 3.5–5 *mg/dL*)	3.8 ± 0.1	3.8 ± 0.1	NS
Serum creatinine level (normal range, 0.8–1.2 *mg/dL*)	0.8 ± 0.0	0.9 ± 0.1	NS
Prothrombin time (normal range, 10.5–13.5 *s*)	11.6 ± 0.2	11.3 ± 0.3	NS
Platelet count (normal range, 150–450 *thou/cu mm*)	155 ± 11	193 ± 15	NS
Mayo risk score	4.6 ± 0.2	5.0 ± 0.4	NS
MELD score	9 ± 0.6		
Esophageal varices			
None	57/91 (62.6%)	19/36 (52.8%)	NS
Small	15/91 (16.5%)	7/36 (19.4%)	NS
Large	19/91 (20.8%)	10/36 (27.8%)	NS
Histologic stage[b]			
1–2	38/80 (47.5%)	12/33 (36.4%)	NS
3–4	42/80 (52.5%)	21/33 (63.6%)	NS

NOTE. Values expressed are median ± SE or number (%).
[a]AMA titer was not available for 5 patients in the study group and 3 patients in the cross-validation group.
[b]Liver biopsy was available for 80 patients in the study group and 33 patients in the cross-validation group.

esophageal varices.[29] For those patients with all 3 variables, the probability of varices was 88%. Nevertheless, the predictive value of each variable was not discussed and the external validity of these tests was not assessed.

The availability of noninvasive predictors of esophageal varices would allow for patient selection even in the absence of histology data, and would facilitate the decision-making process regarding the timing of a screening EGD in patients who had a liver biopsy performed several years prior, especially in view of the delayed progression of PBC in patients treated with UDCA. Also, strong evidence exists to suggest that portal hypertension may develop in precirrhotic patients with PBC. Given the fact that a liver biopsy may not be available or needed for every patient with PBC, and that universal primary prophylaxis with β-blockers is not an effective strategy,[30] noninvasive markers of esophageal varices still are desired. Thus, the primary aims of our study were as follows: (1) to determine the prevalence of esophageal varices in patients with PBC, (2) to evaluate noninvasive markers of esophageal varices in such a population, and (3) to validate our results in an independent set of patients with PBC.

Patients and Methods

Patient Population

A total of 210 patients with a diagnosis of PBC seen at the University of Florida (Gainesville, FL) for the first time between January 1, 1998, and December 31, 2004, were included in the present study. The year 1998 was selected because UDCA was approved by the Food and Drug Administration as standard ther-

Table 2. Predictors of Esophageal Varices by Univariate Analysis in 91 Patients With PBC

Variable	Patients with esophageal varices (n = 34)	Patients without esophageal varices (n = 57)	*P* value
Females	31 (91%)	53 (93%)	NS
Age, *y*	58.8 ± 1.8	56.2 ± 1.3	NS
Serum total bilirubin level (normal range, 0.0–1.0 *mg/dL*)	2.8 ± 0.9	1.6 ± 0.6	<.0001
Serum albumin level (normal range, 3.5–5 *mg/dL*)	3.5 ± 0.1	3.9 ± 0.1	.003
Serum alkaline phosphatase level (normal range, 35–129 *U/L*)	336 ± 33	336 ± 35	NS
Serum aspartate aminotransferase levels (normal range, 0–37 *U/mL*)	89 ± 10	71 ± 7.0	NS
Serum alanine aminotransferase levels (normal range, 0–41 *U/mL*)	75 ± 12	76 ± 8.6	NS
Platelet count (normal range, 150–450 *thou/cu mm*)	122 ± 11	221 ± 14	<.0001
Prothrombin time (normal range, 10.5–13.5 *s*)	12.5 ± 0.3	11.1 ± 0.3	.0025
Mayo risk score	6.0 ± 0.3	4.5 ± 0.3	.0003
MELD score	12 ± 1	8 ± 1	.012

NOTE. Values expressed as mean ± SE or number (%).