ORIGINAL INVESTIGATION

Risk Factors for the Presence of Varices in Cirrhotic Patients Without a History of Variceal Hemorrhage

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Background: Current medical management dictates that all cirrhotic patients without a history of variceal hemorrhage undergo endoscopic screening to detect large varices. However, referral for endoscopic screening of only patients at highest risk for varices may be most cost-effective. The aim of this case-control study was to identify clinical, laboratory, and radiologic findings that predict the presence of varices in patients with cirrhosis.

Methods: Three hundred patients without a history of variceal hemorrhage underwent upper endoscopy as part of an evaluation before liver transplantation. Cases defined as the presence of any varices and cases defined as the presence of large varices were used for examining the risks associated with finding varices on upper endoscopy. Logistic regression was performed to evaluate associations between the presence of varices and patient characteristics.

Results: Platelet count and Child-Pugh class were independent risk factors for the presence of any varices and the presence of large varices. For the presence of any varices, a platelet count of $90 \times 10^3/\mu L$ or less (odds ratio [OR], 2.4; 95% confidence interval [CI], 1.4-4.0) and advanced Child-Pugh class (OR, 3.0; 95% CI, 1.6-5.6) were independent risk factors. For large varices, a platelet count of $80 \times 10^3/\mu L$ or less (OR, 2.3; 95% CI, 1.4-3.9) and advanced Child-Pugh class (OR, 2.8; 95% CI, 1.3-5.8) were independent risk factors associated with varices.

Conclusions: Low platelet count and advanced Child-Pugh class were associated with the presence of any varices and with large varices. These factors allow identification of a subgroup of cirrhotic patients who would benefit most from referral for endoscopic screening for varices.

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CHRONIC LIVER disease is the 10th leading cause of death in adults in the United States, accounting for approximately 25 000 deaths annually (1% of all deaths).[1] Cirrhosis is considered the most advanced stage of chronic liver disease. Several complications are related to advanced liver disease, including the development of variceal hemorrhage, portosystemic encephalopathy, and ascites. Variceal hemorrhage is a consequence of the development of portal hypertension, which is the most common and severe complication in patients with cirrhosis of the liver. Portal hypertension develops in cirrhosis because of an increase in splanchnic blood flow secondary to vasodilation within the splanchnic vascular bed and because of increased resistance to the passage of blood through the liver.[2]

After varices have developed, one third of all patients die of bleeding gastroesophageal varices.[3,4] The risk of initial bleeding from varices is 25% to 35% in 2 years, with most first-bleeding episodes occurring within a year of detection of varices.[5,6] The reported mortality from a first episode of variceal bleeding ranges from 17% to 57%.[7] Of patients who survive the initial episode of bleeding and do not receive active treatment (β-adrenergic blocking agents or endoscopy), two thirds will have another episode of bleeding within 6 months of the initial episode.[7,8] The current belief is that bleeding from varices occurs when the wall of the varix ruptures, and the risk of rupture is related to the wall tension of the varix. Therefore, large varices are more likely to bleed than are small varices.[5,9] Studies by the Northern Italian Endoscopic Club[5] and Zoli et al[10] have shown that the frequency of bleeding from large varices is 50% to 53% compared with 5% to 18% for small varices. In addition, gastric varices also have a high frequency of bleeding (approximately 25%).[11]

To alter these negative statistics, researchers have proposed numerous medical and surgical approaches in the past 2

PARTICIPANTS, MATERIALS, AND METHODS

STUDY DESIGN

This was an unmatched case-control study, with cases and controls selected from patients undergoing liver transplantation evaluation at the OHSU/PVAMC Liver Transplantation Program between January 1, 1995, and September 1, 1999. This study was approved by the institutional review board of Oregon Health Sciences University, Portland. Patients were included in the study if they had not had a history of variceal hemorrhage and were part of the OHSU/PVAMC liver transplantation evaluation database. Two different case and control definitions were used to examine possible risk factors. Initially, cases were defined as cirrhotic patients diagnosed as having large varices on screening upper endoscopy, and controls were cirrhotic patients with small or no varices (these could be considered "clinical" controls because small varices are not considered clinically significant). For the second analysis, cases were defined as patients with any type of varices, and controls were cirrhotic patients without varices ("true" controls).

DEFINITIONS

Screening endoscopies were performed by several endoscopists (A.Z., K.B., and others) who used different classifications to define variceal size. In some cases, endoscopists used the grade (I-IV) classification.[20] In other cases, endoscopists used the "small, medium, or large" classification: small varices flatten with insufflation of the esophageal lumen, medium varices do not flatten with insufflation, and large varices do not flatten with insufflation and are confluent.[17] Most endoscopists classified varices as either small or large (small varices flatten with insufflation or minimally protrude into the lumen and large varices protrude into the lumen and touch each other [presence of confluence] or fill ≥50% of the lumen), as described by De Franchis et al.[21] This simple classification is considered the preferred classification by a recent consensus conference on portal hypertension held in Baveno, Italy.[22] Therefore, when endoscopists used the small, medium, or large classification, medium was reclassified as small; when grades I through IV were used, grades I and II were reclassified as small and grades III and IV were reclassified as large for this study. Gastric varices were classified as either isolated fundic varices or gastroesophageal varices. Because any type of gastric varix is considered a high-risk lesion for bleeding, patients with these lesions were analyzed as cases; in this study, 9 patients had small varices with associated gastric varices, and 4 patients had isolated gastric varices. Analyses were performed with and without gastric varices included in the study group, and no differences were noted in the findings. Therefore, results that include gastric varices are presented. Cirrhosis was defined histologically or by using a combination of laboratory, radiologic, and physical examination findings, as in previous studies.[5]

The liver transplantation database is composed of all patients with cirrhosis undergoing liver transplantation evaluation at OHSU/PVAMC. The database includes physical examination findings, laboratory data, and abdominal ultrasound findings at the time of transplantation evaluation. Because physical examination results can vary from examiner to examiner, physical examination data were

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decades to reduce the incidence of initial variceal bleeding. Portosystemic shunt surgery has been effective in preventing first variceal hemorrhage, but it significantly increases the risk of chronic or recurrent encephalopathy and reduces survival because of perioperative complications.[12-14] The clinical role of prophylactic endoscopic sclerotherapy and band ligation remains unclear. In a recent meta-analysis,[15] cirrhotic patients with large varices and no history of variceal hemorrhage who were given β-adrenergic blocking agents had less chance of variceal bleeding (pooled odds ratio [OR], 0.48) and of dying of bleeding and experienced a trend toward reduction in the total mortality rate compared with patients not given β-adrenergic blocking agents. Based on the results of these studies, the American College of Gastroenterology recommends screening all cirrhotic patients for the presence of esophageal varices and treating patients with large varices with β-adrenergic blocking agents to reduce the incidence of first variceal bleeding.[16] Other investigators[17,18] recommend that screening be performed every 2 years for cirrhotic patients without varices and that patients with known small varices undergo endoscopy every year. However, these guidelines have not been prospectively studied, and their cost-effectiveness has not been demonstrated.

It may be more cost-effective to routinely screen only cirrhotic patients at high risk for the presence of varices. Several studies[5,10,19] have revealed factors that predict risk for first variceal hemorrhage, namely, high Child-Pugh score, variceal size, signs of variceal wall thinning, presence of gastric varices, presence of portal hypertensive gastropathy, and hepatic vein pressure gradient. However, factors that predict the presence of varices are not as well defined. The aim of this study was to identify patient characteristics—including laboratory, radiologic, and physical examination findings—that predict the presence of any varices and the presence of large esophageal varices by using the Oregon Health Sciences University and Portland Veterans Administration Medical Center (OHSU/PVAMC) liver transplantation database of patients with advanced cirrhosis who routinely undergo screening endoscopy as a part of their evaluation.

RESULTS

Between January 1, 1995, and September 1, 1999, 629 cirrhotic patients underwent liver transplantation evaluation. Of these, 300 patients did not have a history of variceal hemorrhage (the study group). All patients were abstinent from alcohol intake for at least 6 months. Patient demographics (overall and by endoscopic findings) are listed in **Table 1**. Most patients (69%) were men, with a mean±SD age of 49.0±7.7 years. Only a few patients (2%) were undergoing any β-adrenergic blocking agent

abstracted only from examinations performed by the 2 transplantation surgeons. Physical examinations were performed in standardized fashion per transplantation evaluation protocol. This database has been maintained since 1991 and contains information on approximately 1200 patients. The results from the first 98 patients in this cohort regarding risk factors predicting the presence of esophagogastric varices were presented previously.[23] This study presents the results from the entire cohort of liver transplantation patients undergoing liver transplantation evaluation at the OHSU/PVAMC Liver Transplant Department between January 1, 1995, and September 1, 1999. All patients were free of gastrointestinal tract complaints, including bleeding; none were taking nonsteroidal anti-inflammatory drugs, acid-suppressing drugs, or β-adrenergic blocking agents; and all were abstinent from alcohol intake for at least 6 months. In addition to recording endoscopic findings, the following data were collected: age, sex, cause of cirrhosis, Child-Pugh class and score, and physical examination findings of splenomegaly, ascites (described as none, nontense, or tense), encephalopathy, and spider angiomata. Also, laboratory data (total bilirubin, aminotransferase, blood urea nitrogen, creatinine, and albumin levels; prothrombin time; and platelet count) and abdominal ultrasound findings (ascites and splenomegaly) were collected.

STATISTICAL ANALYSIS

Statistical analysis was performed using a software package (SPSS 9.0; SPSS Inc, Chicago, Ill). The following model-building strategy was used. After data collection was completed, the distribution of all independent variables was explored. Histograms were generated, and transformations (log transformations, square, square root, etc) were performed when appropriate to normalize the distribution or to identify any natural breaks in the data to facilitate categorization of the data. Then, univariate analysis using logistic regression was applied to identify significant associations with the dependent variable. Transformed and untransformed data were used in the analysis. All analyses were repeated for the 2 case definitions described in the "Study Design" subsection. When cases were defined as having either the presence of any varices or the presence of large varices, binary logistic regression[24] was performed. Any independent variables with associations of $P \leq .2$ then underwent multivariate analysis by simply entering them together using the forward conditional stepwise method and the backward conditional stepwise method. A screening $P = .2$ was used based on model-building strategies proposed by Hosmer and Lemeshow.[24] The following cutoff points were used for the binary and ordinal logistic regression stepwise methods: $P = .05$ for entry into the model and $P = .10$ for removal from the model. Ninety-five percent confidence intervals (CIs) were used in all analyses. The "best" model for each case definition was based on the strength of the model (Hosmer and Lemeshow goodness-of-fit test), its clinical utility, and the biologic plausibility of the model. Any continuous variables included in the final model were then categorized to improve ease of use. Cutoff points were determined using receiver operating characteristic curves, which can determine the "ideal" cutoff points for screening tests in an objective fashion by determining the value that maximizes sensitivity and minimizes 1 – specificity.[25] After the main effects model was generated, confounding factors (any factor that changed the OR of the main effects variables by ≥10%) and interactions were addressed.

or long-acting nitrate therapy before endoscopy. Most patients were in Child-Pugh class B (58%). Fifty-eight percent of patients referred for transplantation had hepatitis C as one of the causes of their liver disease, and 71% had hepatitis C, alcohol, or both as an etiologic factor. Physical examination, laboratory, and radiologic findings are given in **Table 2**. The group without varices had a higher mean platelet count (mean platelet count, 128 500/mm^3) than the group with small varices (mean platelet count, 107 800/mm^3) and the group with large or gastric varices (mean platelet count, 76 500/mm^3). Also, the group without varices had more patients without ascites and encephalopathy than the other groups. Otherwise, the 3 groups had similar physical examination, laboratory, and radiologic findings.

RISK FACTORS FOR THE PRESENCE OF VARICES

The final model had a goodness-of-fit test with $P = .61$, incorporated only 2 variables, and included variables that reflected not only hepatic function (Child-Pugh class) but also portal hypertension (platelet count). To further simplify the model so that it could be easily used in a clinical setting, platelet count was dichotomized using receiver operating characteristic curves. The cutoff platelet count of 90×10^3/μL gave maximum sensitivity of 0.598 and minimum 1 – specificity of 0.379.

With advancing Child-Pugh class, the percentage of patients with varices increased: 29 (44%) of 66 patients in Child-Pugh class A, 129 (74%) of 174 in Child-Pugh class B, and 45 (75%) of 60 in Child-Pugh class C had varices. Also, a significantly higher percentage of patients with platelet counts of 90×10^3/μL or less had varices than did patients with platelet counts greater than 90×10^3/μL (78% vs 56%).

Diuretic use was the only confounding variable; it reduced the OR of the Child-Pugh class by more than 10% when entered into the model. Interaction between the risk factors was not observed. The final model, adjusted for diuretic use, is given in **Table 3**. The data suggest that having a platelet count of 90×10^3/μL or less was associated with a nearly 2½-fold increase in the risk of having varices on upper endoscopy (OR, 2.4; 95% CI, 1.4-4.0) and that Child-Pugh class B or C was associated with a nearly 3-fold increase in the risk of having varices compared with Child-Pugh class A (Child-Pugh class B: OR, 3.0; 95% CI, 1.6-5.6; Child-Pugh class C: OR, 2.7; 95% CI, 1.2-6.1). Using this regression model, the probability of the diagnosis of any varices can be estimated. A cirrhotic patient with a platelet count of 90×10^3/μL or less who is in Child-Pugh class A, B, or C will have a probability of 0.57, 0.81, or 0.82, respectively, of having any varices on upper endoscopy. On the other hand, a cirrhotic patient with a platelet count greater

Table 1. Demographics and Characteristics of Study Participants, Risk Factors for Varices Study, 1999*

	Without Varices (n = 97)	With Small Varices (n = 109)	With Large/Gastric Varices† (n = 94)	Total (N = 300)
Sex, M/F	61/36	74/35	71/23	**206/94**
Age, mean ± SD, y	49.0 ± 7.7	49.0 ± 8.1	50.0 ± 7.3	49.0 ± 7.7
Cause of liver disease				
Hepatitis C	22 (23)	35 (32)	25 (27)	**82** (27)
Hepatitis C/alcohol	29 (30)	33 (30)	31 (33)	**93** (31)
Alcohol	10 (10)	17 (16)	13 (14)	**40** (13)
Hepatitis B	7 (7)	1 (1)	7 (7)	**15** (5)
Hepatitis B/C	0	1 (1)	1 (1)	**2** (1)
PBC/PSC	18 (19)	9 (8)	4 (4)	**31** (10)
Metabolic	1 (1)	1 (1)	1 (1)	**3** (1)
Other	7 (7)	5 (5)	7 (7)	**19** (6)
Cryptogenic	3 (3)	7 (6)	5 (5)	**15** (5)
Medication use				
β-Adrenergic blocking agent	4 (4)	2 (2)	1 (1)	**7** (2)
Long-acting nitrate	0	0	0	**0**
Diuretic‡	52 (54)	72 (66)	70 (74)	**194** (65)
Child-Pugh classification (score)§				
A (5-6)	37 (38)	19 (17)	10 (11)	**66** (22)
B (7-9)	45 (46)	62 (57)	67 (71)	**174** (58)
C (10-15)	15 (16)	28 (26)	17 (18)	**60** (20)

*Data are given as numbers (percentages) except where indicated otherwise. PBC/PSC indicates primary biliary cirrhosis and primary sclerosing cholangitis.
†Four patients had isolated gastric varices, 9 had gastric varices associated with small esophageal varices, and 20 had gastric varices associated with large varices.
‡$P = .01$ by χ^2 test.
§$P < .001$ by χ^2 test.

than $90 \times 10^3/\mu L$ who is in Child-Pugh class A, B, or C will have a probability of 0.36, 0.65, or 0.66, respectively, of having any varices on upper endoscopy.

RISK FACTORS FOR THE PRESENCE OF LARGE VARICES

The final model had a goodness-of-fit test with $P = .25$, incorporated only 2 variables, and included variables that reflected not only hepatic function (Child-Pugh class) but also portal hypertension (platelet count). To further simplify the model for use in a clinical setting, platelet count was categorized using receiver operating characteristic curves. The cutoff platelet count of $80 \times 10^3/\mu L$ gave maximum sensitivity of 0.624 and minimum 1 – specificity of 0.326.

With advancing Child-Pugh class, the percentage of patients with large varices increased: 10 (15%) of 66 patients in Child-Pugh class A, 68 (39%) of 174 in Child-Pugh class B, and 17 (28%) of 60 in Child-Pugh class C had large varices. Also, a significantly higher percentage of patients with platelet counts of $80 \times 10^3/\mu L$ or less had large varices than did patients with platelet counts greater than $80 \times 10^3/\mu L$ (43% vs 22%) (**Table 4**).

Confounding by the other variables was not observed. Also, interaction between the main effects variables was not observed. When Child-Pugh class was kept as a 3-category variable, Child-Pugh class C was not independently associated with the presence of large varices ($P = .28$). This may be because not enough patients were in Child-Pugh class C in the study and fewer of them had large varices compared with patients in Child-Pugh class B. Because of this, Child-Pugh class was further categorized into a binary variable: Child-Pugh class A vs Child-Pugh class B or C, where 10 of 66 patients in Child-Pugh class A had large varices compared with 85 of 234 in Child-Pugh class B or C. The final model is given in Table 4. Similar to the model assessing for the presence of varices, the data suggest that having a platelet count of $80 \times 10^3/\mu L$ or less is associated with a nearly 2½-fold increase in the risk of having large varices on upper endoscopy (OR, 2.3; 95% CI, 1.4-3.9) and that being in Child-Pugh class B or C is associated with a nearly 3-fold increase in the risk of having large varices compared with being in Child-Pugh class A (Child-Pugh class B or C: OR, 2.8; 95% CI, 1.3-5.8). The probability of finding large varices, using this regression model, can be estimated based on the independent variables. A cirrhotic patient with a platelet count of $80 \times 10^3/\mu L$ or less and in Child-Pugh class A or class B or C will have a probability of 0.24 or 0.46, respectively, of having large varices on upper endoscopy. A cirrhotic patient with a platelet count greater than $80 \times 10^3/\mu L$ and in Child-Pugh class A or class B or C will have a probability of 0.12 or 0.27, respectively, of having large varices on upper endoscopy.

COMMENT

The study findings suggest that low platelet count and advanced Child-Pugh class are independent risk factors for the presence of not only large varices but also of any varices in cirrhotic patients. Among clinical, laboratory, and radiologic findings, only platelet count and Child-Pugh class were independent risks. A platelet count of $90 \times 10^3/\mu L$ or less was associated with a nearly 2½-fold increase in the risk of having any varices on upper endoscopy, and being

Table 2. Physical Examination, Laboratory, and Radiologic Findings of Study Participants, Risk Factors for Varices Study, 1999*

	Without Varices (n = 97)	With Small Varices (n = 109)	With Large/Gastric Varices† (n = 94)	Total (N = 300)
Physical examination, No. (%)				
Ascites‡				
None	55 (57)	48 (44)	33 (35)	**136** (45.3)
Nontense	40 (41)	54 (50)	55 (59)	**149** (49.7)
Tense	2 (2)	7 (6)	6 (6)	**15** (5.0)
Splenomegaly	45 (46)	42 (39)	40 (43)	**127** (42.3)
Encephalopathy‡				
None	64 (66)	58 (53)	43 (46)	**165** (55.0)
Mild	33 (34)	50 (46)	51 (54)	**134** (44.7)
Severe	0	1 (1)	0	**1** (0.3)
Spider angiomas	59 (61)	64 (59)	63 (67)	**186** (62.0)
Laboratory data, mean (SD)				
Total bilirubin, mg/dL§	3.0 (4.4)	2.7 (2.5)	2.4 (1.6)	2.7 (3.1)
AST, U/L	95.5 (73.2)	115.9 (86.1)	101.3 (78.7)	104.7 (80.0)
ALT, U/L	80.1 (75.7)	86.4 (72.2)	81.6 (71.4)	82.9 (72.9)
Albumin, g/dL	3.2 (0.7)	2.9 (0.6)	3.0 (0.6)	3.1 (0.6)
Urea nitrogen, mg/dL‖	16.1 (11.6)	15.3 (8.4)	14.6 (6.9)	15.3 (9.2)
Creatinine, mg/dL¶	1.2 (0.9)	1.0 (0.6)	1.0 (0.3)	1.1 (0.66)
Platelet count $\times 10^3/\mu L$#	128.5 (76.7)	107.8 (70.1)	76.5 (32.2)	104.7 (66.5)
Prothombin time, s	14.1 (2.1)	14.4 (92.4)	14.1 (1.4)	14.2 (2.0)
Abdominal ultrasound, No. (%)				
Splenomegaly	60 (62)	66 (61)	69 (73)	**195** (65.0)
Ascites				
None	54 (56)	51 (47)	35 (37)	**140** (47.0)
Small	40 (41)	49 (45)	52 (55)	**141** (47.0)
Large	3 (3)	9 (8)	7 (8)	**19** (6.0)

*AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.
†Four patients had isolated gastric varices, 9 had gastric varices associated with small esophageal varices, and 20 had gastric varices associated with large varices.
‡$P = .04$ by χ^2 test.
§To convert total bilirubin from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 17.1.
‖To convert urea nitrogen from milligrams per deciliter to millimoles per liter of urea, multiply milligrams per deciliter by 0.357.
¶To convert creatinine from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 88.4.
#Two-tailed $P<.001$ by analysis of variance. Tukey HSD (honestly significant difference) post hoc test revealed that the large/gastric varices group's mean platelet count was significantly different from that of the other 2 groups.

Table 3. Results of Binary Logistic Regression Analysis for Risk Factors for the Presence of Varices, Adjusted for Confounders, Risk Factors for Varices Study, 1999

Variable	Coefficient (SE)	2-Sided *P* Value	Adjusted Odds Ratio (95% Confidence Interval)*	Difference Associated With Odds Ratio
Platelet count	0.8677 (0.2649)	<.001	2.40 (1.43-4.01)	Platelet count $\leq 90 \times 10^3/\mu L$ vs $>90 \times 10^3/\mu L$
Child-Pugh class	1.1109 (0.3134)	<.001	3.04 (1.64-5.61)	Child-Pugh class B vs A
	1.0082 (0.4098)	.003	2.74 (1.23-6.12)	Child-Pugh class C vs A

*Adjusted for diuretic use.

Table 4. Results of Binary Logistic Regression Analysis for Risk Factors for the Presence of Large Varices, Risk Factors for Varices Study, 1999

Variable	Coefficient (SE)	2-Sided *P* Value	Odds Ratio (95% Confidence Interval)	Difference Associated With Odds Ratio
Platelet count	0.8541 (0.2596)	.001	2.30 (1.41-3.85)	Platelet count $\leq 80 \times 10^3/\mu L$ vs $>80 \times 10^3/\mu L$
Child-Pugh class	1.0119 (0.3757)	.007	2.75 (1.32-5.75)	Child-Pugh class B/C vs A

in Child-Pugh class B or C was associated with a nearly 3-fold increase in the risk of having varices compared with being in Child-Pugh class A. A platelet count of $80 \times 10^3/\mu L$ or less was associated with a nearly 2½-fold increase in the risk of having large varices on upper endoscopy, and being in Child-Pugh class B or C was associated with a nearly 3-fold increase in the risk of having large varices compared with being in Child-Pugh class A.

Probability estimates for the presence of any varices, based on platelet count and Child-Pugh class, ranged

from 0.36 if the patient was in Child-Pugh class A and had a platelet count greater than 90×10^3/μL to a probability of 0.82 if the patient was in Child-Pugh class C and had a platelet count of 90×10^3/μL or less. The probability estimates for the presence of large varices ranged from 0.12 if the patient was in Child-Pugh class A and had a platelet count greater than 80×10^3/μL to a probability of 0.46 if the patient was in Child-Pugh class B or C and had a platelet count of 80×10^3/μL or less. This suggests that cirrhotic patients who are in Child-Pugh class A and have a platelet count greater than 80×10^3/μL may not benefit from screening because their probability of having large varices on upper endoscopy is low.

Few studies have been performed to evaluate clinical, laboratory, and radiologic factors that are strongly associated with the presence of varices. Cales et al[17] report that of 84 patients, 16 without varices (19%) and 35 with small varices (42%) developed large varices during 16-month follow-up. In their study, multivariate analysis revealed that initial size of varices and interval worsening of the Child-Pugh score predicted the development of varices. In a logistic regression study by Garcia-Tsao et al[26] of 180 patients, the presence of spider angiomata, a low albumin level, and a low platelet count were independent risk factors for the presence of varices. Chalasani et al[27] found that of 346 patients, the presence of splenomegaly on physical examination (OR, 2.0; 95% CI, 1.1-3.8) and a platelet count less than 88×10^3/μL (OR, 1.6; 95% CI, 1.0-3.0) were independent risk factors for the presence of large varices. Finally, in a study by Pilette et al,[28] of 116 patients with cirrhosis, a low platelet count, high prothrombin time, and the presence of spider angiomata were independent risk factors for the presence of varices.

In the present study, as in previous studies, low platelet count and advanced Child-Pugh class were risk factors for the presence of both any varices and large varices. Child-Pugh class is a well-validated classification for the degree of hepatic function in patients with cirrhosis. Because portal hypertension is a consequence in part of the generalized vasodilation and the hyperdynamic splanchnic and systemic circulatory state,[2] the degree of hepatic function likely affects the development of portal hypertension via humoral factors and, therefore, the development of varices. The association of platelet count to the presence of varices is probably a reflection of the degree of portal hypertension and possibly other factors. The cause of splenomegaly in cirrhotic patients is likely owing to the hemodynamic changes associated with portal hypertension.[29] Historically, splenic sequestration or antibody-mediated destruction of platelets have been believed to be the cause of thrombocytopenia in patients with cirrhosis.[30,31] However, recent studies have implicated reduced hepatic production of liver-derived thrombocytopoietic growth factor thrombopoietin as a major factor for thrombocytopenia in cirrhosis of the liver.[32,33]

This study has several potential limitations. We evaluated only liver transplantation candidates. Therefore, the findings may not be generalizable to all cirrhotic patients. Also, because the data were collected retrospectively, misclassification of the outcome was possible. To minimize misclassification, every effort was made to review the endoscopic reports and, when possible, photographs of the findings. Furthermore, analysis was conducted not only defining a case as the presence of large varices but also defining a case as the presence of any varices (the presence of any varices is difficult to misclassify). The same risk factors were identified for both case definitions, suggesting that even when cases were defined as large varices, misclassification was likely minimal. The only difference was a platelet count cutoff value that was lower for detecting the presence of large varices (80×10^3/μL compared with 90×10^3/μL). This lower platelet count cutoff value for large varices seems plausible because the degree of thrombocytopenia seems to be associated with the degree of portal hypertension and likely the size of varices. Bias related to exposure history was minimized by the fact that all exposure data were gathered in a standardized fashion based on the liver transplantation evaluation protocol. In addition, several precautions were undertaken to limit data abstraction bias. Data abstraction was performed by only one person (A.Z.) to minimize variability in medical record abstraction. Endoscopic findings were collected on different days than clinical and radiologic data, and the 2 sets of data were initially placed in different databases to prevent the data abstractor from linking the independent and dependent variables and potentially biasing the data abstraction procedure. Finally, the data were directly recorded in an electronic database to reduce transcription errors.

In conclusion, our data suggest that low platelet count and advanced Child-Pugh class are independent risk factors for the presence of any varices and for the presence of large varices. For the presence of any varices, cirrhotic patients with platelet counts of 90×10^3/μL or less are nearly 2½ times more likely to have varices on upper endoscopy than are patients with a platelet count greater than 90×10^3/μL; patients in Child-Pugh class B or C are nearly 3 times more likely to have varices on upper endoscopy than are patients in Child-Pugh class A. Similarly, for the presence of large varices, cirrhotic patients with platelet counts of 80×10^3/μL or less are nearly 2½ times more likely to have large varices on upper endoscopy than are patients with a platelet count greater than 80×10^3/μL; patients in Child-Pugh class B or C are nearly 3 times more likely to have large varices on upper endoscopy than are those in Child-Pugh class A.

Probability estimates based on logistic regression models using these risk factors can stratify patients into low- or high-risk groups for having varices. Risk stratification based on these risk factors may help clinicians identify patients who would most likely benefit from referral for screening for gastroesophageal varices. These findings, including the validity of the models, need to be verified with prospectively collected data. Also, cost-effectiveness analysis should be performed to determine which strategy is best: screening all cirrhotic patients vs screening only high-risk patients vs no screening.

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