RISK FACTORS FOR THE PRESENCE OF VARICES IN CIRRHOTIC PATIENTS WITHOUT A HISTORY OF VARICEAL HEMORRHAGE

by

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THESIS

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CERTIFICATE OF APPROVAL

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Precis

Since my days as a Gastroenterology fellow at Oregon Health Sciences University, I have had an interest in liver disease. It was unforgettable the first time that I managed a patient with cirrhosis and variceal hemorrhage. It was not only "exciting", but also quite frightening. These patients are very ill and despite advances in the endoscopic technology used to manage this type of bleeding, morbidity and mortality rates are still quite high.

As I progressed in my training I became interested in clinical research, specifically outcomes research related to liver disease. Because this area is still in its infancy, it is new and exciting and offers many opportunities to do important work. However, I realized as I completed my fellowship that to excel at clinical investigation, I would need formal training in study design, epidemiology, and biostatistics. Therefore, as I joined the faculty in the Division of Gastroenterology and Hepatology at OHSU, I also began my MPH studies.

During my MPH training, I learned a great deal about the importance of prevention of disease and its complications, and I developed the tools I would need to perform clinical research. Prevention of liver disease and its complications is becoming very important in the field of Hepatology. Because of my unforgettable experiences in my fellowship, I naturally developed an interest in variceal hemorrhage. Recently the prevention of the first variceal hemorrhage in cirrhotic patients has received special attention in the Hepatology literature. Current recommendations are that all cirrhotic patients undergo screening upper endoscopy to detect large varices, as they patient at high risk for bleeding, and if found, to treat them pharmacologically. As one can imagine,

performing endoscopy on all these patients would be very expensive and not without risk. To non-invasively identify patients at highest risk for the presence of large varices and subsequently perform enodoscopy only on them would likely be more cost-effective. With this reasoning in hand, and a large database of patients who underwent screening upper endoscopy as part of liver transplant evaluation, that I undertake this project.

ABSTRACT

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

Methods: Three hundred (300) patients without a history of variceal hemorrhage underwent upper endoscopy as part of a pre-liver transplant evaluation. Two different case definitions, 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. Univariate/multivariate analysis using logistic regression was used to evaluate associations between the presence of varices and patient characteristics including: etiology of liver disease, Child-Pugh class, physical findings (spider angiomata, splenomegaly, and ascites), encephalopathy, laboratory parameters (prothrombin time, albumin, bilirubin, blood urea nitrogen, creatinine, and platelets), and abdominal ultrasound findings (portal vein diameter and flow, splenomegaly, and ascites).

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, platelet count $\leq$90,000/mm^3(OR=2.4; 95% CI 1.43-4.01) and advanced Child-Pugh class (OR=3.04; 95% CI 1.64-5.61) were independent risk factors. For large varices, platelet

count $\leq$80,000/mm^3 (OR=2.3; 95% CI 1.41-3.85) and advanced Child-Pugh class (OR=2.75; 95% CI 1.32-5.75) were independent risk factors associated with varices.

Conclusions: A low platelet count and advanced Child-Pugh class were associated with the presence of any varices and with large varices. A large prospective study is needed to verify and validate these findings and may allow identification of a subgroup of patients that would most benefit from endoscopic screening for varices.

INTRODUCTION

Chronic liver disease is the tenth leading cause of death among adults in the United States. It accounts for approximately 25,000 deaths annually (1% of all deaths) (1). Cirrhosis is considered the most advanced stage of chronic liver disease. There are several complications 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 of 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).

The development of esophageal varices due to portal hypertension is not only common in patients with cirrhosis, but also, potentially life-threatening. In a study by Cales et al, among patients with well compensated cirrhosis (mainly alcoholic) initially without varices, 23% developed varices at 1 year and 50% at 2 years (3). Among patients with small varices, 42% progressed to large varices during a mean follow up of 16 months (3). In another study dealing primarily with patients with Hepatitis C, 16% developed varices at 2 years and 30% at 6 years (4).

After varices have developed, one third of patients will die of bleeding gastroesophageal varices (5,6). The risk of bleeding from varices is 25-35% over a two year period with the majority of initial episodes of bleeding occurring within a year from the time of detection of varices (7,8). The reported mortality from a first episode of variceal bleeding ranges between 17-57% (9). Among patients who survive the initial

episode of bleeding and do not receive active treatment (beta-blocker or endoscopic therapy), two thirds will have another episode of bleeding within 6 months of the initial episode (9,10). 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 clearly more likely to bleed than small (7,11). Studies by the Northern Italian Endoscopic Club and by Zoli et al have shown that the frequency of bleeding from large varices is between 50-53%, compared to 5-18% for small varices (7,12). In addition, Sarin et al have shown that gastric varices also have a high frequency of bleeding, approximately 25% (13).

In an attempt to alter these grim statistics, researchers have proposed numerous medical and surgical approaches in the last two decades to reduce the incidence of the initial variceal bleed. Portosystemic shunt surgery has been shown to be very effective in preventing variceal hemorrhage, but it significantly increases the risk of chronic or recurrent encephalopathy and reduces survival because of perioperative complications. (14-16). The clinical role of prophylactic endoscopic sclerotherapy and band ligation remains unclear. In a recent meta-analysis, cirrhotic patients with large varices and no history of variceal hemorrhage who were given beta-blockers had less chance of variceal bleeding (pooled odds ratio of 0.48) and of dying from bleeding, and experienced a trend toward a reduction in total mortality over patients not given beta-blockers (17). In addition, emerging data suggest that adding long-acting nitrates to beta-blocker therapy may further reduce bleeding rates (18). Based on these reports, the American College of Gastroenterology recommends screening all cirrhotic patients for the presence of esophageal varices and treating patients with large varices with beta-blockers to reduce

the incidence of first variceal bleed (19). Other investigators, based on natural history data, have recommended that screening be repeated every two years for cirrhotic patients without varices and that patients with known small varices be endoscoped every year (3,20). However, these guidelines have not been prospectively studied nor has their cost-effectiveness been demonstrated.

It may be more cost-effective to routinely screen only cirrhotic patients at high risk for the presence of varices. Several studies have revealed factors that predict the 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 (7,12,21). However, the factors that predict the presence of varices are not as well defined.

The Oregon Health Sciences University and Portland VA Medical Center (OHSU/VAMC) liver transplant program maintains a large database of patients undergoing liver transplant evaluation. These patients represent cirrhotics with advanced liver disease. Routinely these patients undergo screening endoscopy to assess for the presence of varices as a part of their evaluation. In addition, they undergo comprehensive physical, laboratory, and radiologic examinations. The aim of this study is 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 using this database of patients with advanced cirrhosis. Then using logistic regression modeling techniques, incorporating independent predictor variables, I examined factors associated with the presence of varices of any size, and the presence of large varices, in cirrhotic patients.

Null Hypothesis

No clinical, laboratory, or radiologic findings will predict the presence of varices in cirrhotic patients without a previous history of variceal hemorrhage.

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/VAMC Liver Transplant Department between January 1995 and September 1999. This study was approved by the Institutional Review Board of Oregon Health Sciences University. Patients were included in the study if they had not had a previous history of variceal hemorrhage, and were a part of the Liver Transplant Evaluation Database. Two different case-control definitions were used to examine possible risk factors. Initially, cases were defined as cirrhotic patients diagnosed with large varices on screening upper endoscopy, while controls were cirrhotic patients with small or no varices (these could be considered "clinical" controls, since small varices are not considered to be clinically significant). For the second analysis, cases were defined as patients found to have any type of varices, while controls were cirrhotic patients with no varices ("true" controls).

Definitions. Screening endoscopies were performed by several endoscopists who used different classifications to define variceal size. In some cases, endoscopists used the Grade I-IV classification (22). In other cases, endoscopists used the small, medium, or large classification where 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 (3). The majority of endoscopists classified varices as either small or large (small varices flatten with insufflation or they minimally protrude into the lumen and large varices protrude into the lumen and touch each other [presence of confluence] or they fill at least 50% of the lumen) as described by De Franchis et al (23). This simple classification is considered the preferred classification by a recent Consensus Conference on Portal Hypertension held in Baveno, Italy (24). Therefore, when endoscopists used the small, medium, and large classification, medium was reclassified as small; and when Grades I-IV was used Grades I-II were reclassified as small and Grades III-IV were reclassified as large for this study. Gastric varices were classified as either isolated fundic varices or gastroesophageal varices. Since any type of gastric varices are considered high risk lesions 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 with gastric varices will be presented. Cirrhosis was defined histologically or by a combination of laboratory, radiologic, and physical examination findings as in previous studies (7).

The Liver Transplant Database is comprised of all patients with cirrhosis undergoing liver transplant evaluation at OHSU/VAMC. The database includes physical examination findings, laboratory data, and an abdominal ultrasound findings at the time of transplant evaluation. Since physical examination results can vary from examiner to examiner, physical examination data were abstracted only from the examinations

performed by the two transplant surgeons. Physical examinations were performed in a standardized fashion per transplant evaluation protocol.

This database has been maintained since 1991 and contains data on approximately 1200 patients. Using the initial history and physical examination report, ultrasound report, initial laboratory results, and screening endoscopy report (all these are usually obtained within 1 month of each other), I collected the following data:

Demographics:
- Age at time of endoscopy
- Gender
- Etiology of cirrhosis

Physical manifestations of liver disease:
- Splenomegaly (y/n)
- Ascites (none, non-tense, tense)
- Encephalopathy (none, mild, severe)
- Spider angiomata (y/n)

Laboratory data:
- Total bilirubin
- Albumin
- Prothrombin time
- Platelet count
- AST
- ALT
- Blood urea nitrogen
- Creatinine

Radiologic manifestations of liver disease:
- Ascites (none, small, large amount)
- Splenomegaly (y/n)

Assessment of liver dysfunction:
- Modified Child-Pugh class and score (see Table 1in the Appendix)

Sample Size and Power Calculations

Pilot data collected from this dataset, in addition to information from the literature, were used to determine the estimated sample sizes necessary for this study.

Initially, pilot data had been collected on patients evaluated from January 1995 through June 1997 (data before 1995 were not used due to difficulty in obtaining this archived data and reliability issues). Ninety-eight (98) patients were eligible and had complete datasets. Of these, 68% (67 of 98) of patients had varices with 30% of them (20 of 67) having large varices. In addition, using the natural history data on 494 cirrhotic patients reported by Pagliaro et al (4), I calculated the following sample size. If we use Child-Pugh class (Class A [no exposure] versus Class B/C[positive exposure]) as the exposure of interest—it is a well validated (25) classification for the degree of liver disease—and either the presence of varices (first case definition) or the presence of large varices (second case definition) as the outcome of interest, the following estimates were obtained. If the presence of varices is the outcome of interest, 18% of patients without varices (control group) will be Childs B/C. If the study is powered to detect an odds ratio of 2.5 (since in general an odds ratio $\geq$2.5 is considered to be of clinical significance and therefore, important to detect) with a Power of 80% at an alpha of 0.05, one needs 111 cases (patients with varices) and 111 controls (patients without varices). If the presence of large varices is the outcome of interest, 21% of patients without large varices will be Childs B/C. Therefore, to obtain a Power of 80% and an alpha of 0.05, one needs 102 cases (patients with large varices) and 102 controls (patients with no varices or small varices) to detect an odds ratio of 2.5 or greater.

Statistical Analysis

Statistical analysis was performed using SPSS 9.0 software package (SPSS Inc., 1999) and JMP Statistical Discovery Software 3.2.1 (SAS Institute Inc., 1997). The

Kappa statistic was used to evaluate inter-observer agreement (such as ascites determined by physical examination and ultrasound). As suggested by Landis et al (26) a kappa greater than 0.75 represents excellent agreement beyond chance and a kappa value below 0.4 represents poor agreement. Univariate and multivariate analysis using logistic regression was performed to identify significant risk factors for the presence of any varices and the presence of large varices. Significance level was set at 0.05.

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 and/or in order to identify any natural breaks in the data to facilitate categorization of the data. Then univariate analysis using logistic regression was used to identify significant associations with the dependent variable. Both transformed and untransformed data were used in the analysis (Table 2 in the Appendix). All analyses were repeated for the two case definitions described previously. When the cases were defined as either the presence of any varices or the presence of large varices, binary logistic regression (27) was performed. In addition to binary logistic regression, ordinal logistic regression (28) was used to study associations between the independent variables and the dependent variable when the dependent variable was defined as having three possible states—no varices, small varices or large varices. Any independent variables whose associations had p-values 0.2 or less then underwent multivariate analysis by simply entering them together, by Forward Conditional stepwise method, and by Backward Conditional stepwise method. A screening p-value of 0.2 was used based on model-building strategies proposed by

Hosmer and Lemeshow (27). The following cutoffs were used for the binary and ordinal logistic regression stepwise methods: a p-value of 0.05 for entry into the model and a p-value of 0.10 for removal from the model. Ninety-five percent confidence intervals 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 its ease of use. Cut-off points were determined using Receiver Operator Characteristic (ROC) curves. ROC curves can determine the "ideal" cutoff points of screening tests in an objective fashion by determining the value that maximizes sensitivity and minimizes 1-specificity (29). After the main-effects model was generated, confounding factors (any factor that changed the odds ratio of the main-effects variables by 10% or more) and interactions were addressed.

RESULTS

Between January of 1995 and September of 1999, 629 cirrhotic patients underwent liver transplant evaluation. Of these, 300 patients did not have a previous history of variceal hemorrhage. These patients made up the study group. All patients were abstinent from alcohol for at least 6 months. Patient demographics are listed in Table 1. The majority of the patients were male (69%) with a mean age of 49 years (standard deviation $\pm$7.7). Only a minority (2.3%) of patients were on any beta-blocker or long-acting nitrate therapy prior to endoscopy. The majority of patients were Child-Pugh Class B (58%). Etiology of liver disease is also shown in Table 1. Fifty-eight (58) percent

of patients referred for transplantation had Hepatitis C as one of the etiologies of their liver disease; and 71% of patient had either Hepatitis C and/or alcohol as an etiologic factor. Physical examination, laboratory, and radiologic findings are shown 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/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 three groups had similar physical examination, laboratory, and radiologic findings. Also, there was good agreement between ascites determined by physical exam and by ultrasound (Kappa value of 0.73). Splenomegaly, however, was under-reported by physical examination as compared to by ultrasound (kappa of 0.4). Table 3 shows the endoscopic findings. No varices were seen in 32.3% of patients, while 31.3% of patients had large varices. Isolated gastric varices were seen in only 1.3% of patients. Figures 1-14 in the Appendix show histograms of the laboratory values. Potential cutoff values were determined using histograms of transformed and untransformed data. See Table 2 in the Appendix for the final cutoff values used for regression analysis.

Risk Factors for the Presence of Varices

Table 3 in the Appendix shows the univariate analysis using binary logistic regression. The independent variables that were associated with the outcome with a p-value ≤ 0.2 then underwent multivariate analysis to determine which were independent risk factors for the presence of varices. Transformed variables were not placed together

with their untransformed counterparts into the same multivariate analysis. Instead, several multivariate logistic models were evaluated with combinations of different transformed and untransformed variables. Table 4 in the Appendix shows the final models determined by manually entering and removing variables (using a p-value ≤ 0.2), by Forward Conditional stepwise method, and by Backward Conditional stepwise method. Model 1 had the best fit as determined by the Goodness-of-Fit Test (p-value= 0.6148), incorporated only two variables, and incorporated variables that addressed 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, the variable "platelet count" was categorized using ROC curves. The cutoff at a platelet count of 90,000/mm^3 gave a maximum sensitivity (0.598) and minimum 1-specificity (0.379) (see Figure 1).

The individual relationships between the presence of varices and the two risk factors are shown in Table 4. With advancing Child-Pugh class the percentage of patients with varices increased—43.9% of Child-Pugh class A patients had varices, while 74% of Child-Pugh class B and 75% of Child-Pugh class C patients had varices. Also, a significantly higher percentage of patients with platelet counts less than 90,000/mm^3 had varices than patients with platelet counts greater than 90,000/mm^3 (78% versus 56%).

Diuretic use was the only confounding variable, as it reduced the odds ratio of Child-Pugh class by greater than 10% when entered into the model. Interaction between the risk factors was not observed. The final model, adjusting for diuretic use, is shown in Table 5. This model suggests that having a platelet count $\leq$90,000/mm^3 is associated with nearly a two and a half fold increase in the risk of having varices on upper endoscopy

(OR=2.4 with a 95% CI 1.43-4.01); and that being a Child-Pugh class B or C is associated with nearly a three fold increase in the risk of having varices as compared to being Child-Pugh class A (Child-Pugh class B: OR=3.04 with a 95% CI 1.64-5.61; and Child-Pugh class C: OR=2.74 with a 95% CI 1.23-6.12). Using this regression model, I find that the probability of the diagnosis of any varices can be estimated. A cirrhotic patient with a platelet count less than 90,000/mm^3 who is a 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 than 90,000/mm^3 who is a 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. These probability estimates are similar to the findings among the 300 study subjects (see Table 6).

Risk Factors for the Presence of Large Varices

Table 5 in the Appendix shows the univariate analysis using binary logistic regression for the presence of large varices. Similar to the univariate analysis for the presence of large varices, independent variables that were associated with the outcome variable with a p-value ≤ 0.2 then underwent multivariate analysis to determine which were independent risk factors for the presence of large varices. Then several multivariate logistic models were evaluated with combinations of different transformed and untransformed variables. Table 6 in the Appendix shows the final models determined by manually entering and removing variables (using a p-value ≤ 0.2), by Forward Conditional stepwise method, and by Backward Conditional stepwise method. Model 1 had the best Goodness-of-Fit Test (p-value= 0.2526), incorporated only two variables,

and incorporated a variable that addressed hepatic function (Child-Pugh class), as well as, portal hypertension (platelet count). To further simplify the model for use in a clinical setting, the variable platelet count was categorized using ROC curves. The cutoff of a platelet count of 80,000/mm^3 gave a maximum sensitivity (0.624) and minimum 1-specificity (0.326) (see Figure 2).

The individual relationships between the presence of large varices and the two main effects variables are shown in Table 7. The Table shows that with advancing Child-Pugh class, the percentage of patients with large varices increased—15.2% of Child's A patients had large varices, while 39.1% of Child's B and 28.3% of Child's C patients had large varices. One notes that a lower proportion of Child-Pugh class C patients had large varices (28%) than Child-Pugh class B patients (39%). Also, the Table shows that a significantly higher percentage of patients with platelet counts less than 80,000/mm^3 had large varices than patients with platelet counts greater than 80,000/mm^3 (43% versus 22.4%).

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 three-category variable, Child-Pugh class C was not independently associated with the presence of large varices, p-value=0.28 (see Table 6 in Appendix). This may be due to the fact that not enough patients were Child-Pugh class C in the study and fewer of them had large varices compared to Child-Pugh class B patients. Because of this, Child-Pugh class was further categorized into a binary variable—Child-Pugh class A versus Child-Pugh class B/C, where 10 of 66 patients with Child-Pugh class A had large varices compared to 85 of 149 patients with Child-Pugh class B/C. The final model is shown in Table 8. Similar

to the model assessing for the presence of varices, this model suggests that having a platelet count $\leq 80{,}000/mm^3$ is associated with nearly a two and a half fold increase in the risk of having large varices on upper endoscopy (OR=2.3 with a 95% CI 1.41-3.85); and that being a Child-Pugh class B or C is associated with nearly a three fold increase in the risk of having large varices as compared to being Child-Pugh class A (Child-Pugh class B/C: OR=2.75 with a 95% CI 1.32-5.75). 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 less than $80{,}000/mm^3$ who is a Child-Pugh class A or B/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 $80{,}000/mm^3$ who is a Child-Pugh class A or B/C will have a probability of 0.12 or 0.27 respectively of having large varices on upper endoscopy. These probability estimates are similar to the findings among the 300 study subjects (see Table 9).

Risk Factors for the Presence of No Varices, Small Varices, and Large Varices

To further explore the relationship between the independent variables and the presence of varices, I used ordinal logistic regression to assess for the risk factors for two states: presence of small varices, and the presence of large varices (i.e., the probaility of two events occurring versus only one event occurring as in binary logistic regression). Initially univariate analysis was done to assess for associations with p-values$\leq$ 0.2. Four variables were identified: gender (p-value=0.06), creatinine (p-value=0.0870), platelet count (p-value=0.0002), and Child-Pugh class (p-value=0.0036). Multivariate analysis revealed that platelet count (p-value<0.0001) and Child-Pugh class (p-value=0.0001)

were the only independent risk factors for the presence of two states (both small and large varices). This is similar to the independent risk factors found when using binary logistic regression for the presence of varices in one case and the presence of large varices in the other. Table 7 in the Appendix shows the final ordinal logistic model. These results suggest that the same risk factors, platelet count and Child-Pugh class, are associated with the outcome variable, whether or not it is defined as an ordinal variable (the presence of no varices, small varices, or large varices) or a binary variable (presence of no varices versus any varices or large varices).

DISCUSSION

The findings in this study suggest that a low platelet count and advanced Child-Pugh-class are independent risk factors for the presence of not only large varices, but also the presence of any varices in cirrhotic patients. Among clinical, laboratory, and radiologic findings, only platelet count and Child-Pugh class were found to be an independent risk. Having a platelet count $\leq 90{,}000/mm^3$ was associated with nearly a two and a half fold increase in the risk of having any varices on upper endoscopy; and that being a Child-Pugh class B or C was associated with nearly a three fold increase in the risk of having varices as compared to being Child-Pugh class A. Having a platelet count $\leq 80{,}000/mm^3$ was associated with nearly a two and a half fold increase in the risk of having large varices on upper endoscopy; and that being a Child-Pugh class B/C was associated with nearly a three fold increase in the risk of having large varices as compared to being Child-Pugh class A.

Based on the regression models, probability estimates for the presence of any varices, based on platelet count and Child-Pugh class, ranged from 0.36, if the patient was Child-Pugh class A and had a platelet count greater than 90,000/mm^3, to a probability of 0.82, if the patient was a Child-Pugh class C and had a platelet count less than 90,000/mm^3. The probability estimates for the presence of large varices ranged from 0.12, if the patient was Child-Pugh class A and had a platelet count greater than 80,000/mm^3, to a probability of 0.46, if the patient was a Child-Pugh class B/C and had a platelet count less than 80,000/mm^3. This suggests that cirrhotic patients who are Child-Pugh class A and have a platelet count greater than 80,000/mm^3 may not benefit from screening, since their probability of having large varices on upper endoscopy is low. Furthermore, ordinal logistic regression analysis also identified platelet count and Child-Pugh class as independent risk factors when the outcome was defined as the presence of no varices, small varices, or large varices.

Since the data were collected retrospectively in this study, misclassification of the outcome was a concern. There was variability in grading the size of varices by the endoscopists, therefore for this study, the findings had to be re-categorized into either no varices, small varices, or large varices. However, misclassification of the outcome variable was unlikely when cases were defined as the presence of any varices, since in general it is difficult to misclassify the presence or absence of varices. Even when cases were defined as large varices, misclassification of the outcome variable was likely minimal, since the risk factors identified were similar to the other case definition with the only difference being a platelet cut-off that was lower for detecting the presence of large varices (80,000/mm^3 compared to 90,000/mm^3). This lower platelet count cutoff for large

varices seems plausible, since the degree of thrombocytopenia appears to associated with the degree of portal hypertension and likely the size of varices. Among the risk factor variables, because platelet count was an objective laboratory finding, measurement error was likely minimal. Similarly, Child-Pugh classification likely had minimal measurement error, since four of its five variables were objectively determined.

These findings have important clinical implications in the management of patients with cirrhosis. Variceal hemorrhage is associated with significant morbidity, mortality, and health care costs (30). A recent study showed that the direct costs alone for a single episode of variceal hemorrhage ranges from $15,000 to $20,000 (31). Thus, prevention of first variceal hemorrhage is of critical importance. Recently, the American College of Gastroenterology published guidelines that recommend endoscopic screening for esophageal varices in all cirrhotic patients and treatment of patients with large varices with beta-blocker therapy (19). These guidelines have been accepted by the rest of the gastrointestinal organizations. However, endoscopically screening all cirrhotic patients would utilize a great deal of health care resources in terms of cost and manpower. To screen only certain high risk patients with cirrhosis would reduce the burden on the health care system.

Few studies have been performed to evaluate these clinical, laboratory, and radiologic factors that are strongly associated with the presence of varices. Cales et al reported that, among 84 patients, 19% without varices and 42% with small varices developed large varices over a 16 month follow up period (3). In his study, multivariate analysis revealed that initial size of varices, and interval worsening of the Child-Pugh score predicted the development of varices. In a study by Garcia-Tsao et al (32), of 180

patients using logistic regression the presence of spider angiomata, low albumin, and a low platelet count were independent risk factors for the presence of varices. Chalasani et al (33) found that among 346 patients, the presence of splenomegaly on physical examination (OR=2.0; 95% CI:1.1-3.8) and a platelet count less than 88,000/mm^3 (OR= 1.6; 95% CI:1.04-3.0) were independent risk factors for the presence of large varices. Finally, in a study by Pilette et al of 116 patients with cirrhosis, a low platelet count, a high prothrombin time, and the presence of spider angiomata were independent risk factors for the presence of varices (34).

As described above, both a low platelet count and Child-Pugh class have been shown in one or more previous studies to be a risk factor for either the presence of any varices or large varices. In the present study, they were risk factors for both the presence of any varices and large varices. Child-Pugh class is a well-validated classification for the degree of hepatic function in patients with cirrhosis. Since portal hypertension is a consequence in part to the generalized vasodilatation and the hyperdynamic splanchnic and systemic circulatory state (2), the degree of hepatic function likely influences the development of portal hypertension via humoral factors and therefore, to 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 due to the hemodynamic changes associated with portal hypertension (35). Historically, splenic sequestration or anti-body mediated destruction of platelets have been felt to be the cause of thrombocytopenia in patients with cirrhosis (36,37). However, recent studies have implicated reduced hepatic

production of the liver-derived thrombocytopoietic growth factor thrombopoietin as a major factor for thrombocytopenia in cirrhosis of the liver (38,39).

Several aspects of our study deserve special attention. This study evaluated only liver transplant candidates, which may not reflect all cirrhotic patients in general. These findings, therefore, may not be generalizable to all cirrhotic patients. Also, as this was a retrospective study there was a risk of introducing bias. To standardize the reporting of endoscopic findings, the grading of varices had to be re-catogorized into none, small, or large. To increase the likelihood of uniform interpretation every effort was made to review the endoscopic reports and, when possible, the photographs of the findings. However, as described above, since the presence of any varices is difficult to misclassify, misclassification of the presence of varices was unlikely. Bias related to exposure history is unavoidable in a retrospective study, but was minimized by the fact that all exposure data was gathered in a standardized fashion based on the liver transplant evaluation protocol. In addition, several precautions were undertaken to limit data abstraction bias. Data abstraction was done by only one person (the investigator) in order to minimize variability in chart abstraction. The endoscopic findings were collected on different days from the collection of the clinical and radiologic data, and the two sets of data were initially placed in different databases. This prevented the data abstractor from linking the independent and dependent variables and potentially biasing the data abstraction procedure. Finally, the data was directly recorded into an electronic database to reduce transcription errors.

SUMMARY AND CONCLUSIONS

In conclusion, this case-control study suggests that a 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 less than 90,000/mm^3 are nearly two and a half more times likely to have varices on upper endoscopy than patients with a platelet count greater than 90,000/mm^3; and Child-Pugh class B or C patients are nearly three times more likely to have varices on upper endoscopy than Child-Pugh class A patients. Similarly, for the presence of large varices, cirrhotic patients with platelet counts less than 80,000/mm^3 are nearly two and a half more times likely to have large varices on upper endoscopy than patients with a platelet count greater than 80,000/mm^3; and Child-Pugh class B/C patients are nearly three times more likely to have large varices on upper endoscopy than Child-Pugh class A patients.

Probability estimates based on logistic regression models using these risk factors can stratify patients as either being low or high risk for having varices. Risk stratification based on these risk factors may help clinicians identify patients who would most likely benefit from screening for gastroesophageal varices. These findings, including the validity of the models, need to be verified with prospectively collected data. Therefore, future studies will include collecting clinical, laboratory, and radiologic information prospectively in all cirrhotic patients (both transplant and non-transplant candidates) at Oregon Health Sciences University and the Portland VA Medical Center in order to assess the validity of the present study's findings. Also, cost-effective analysis will be performed to determine which strategy is best, screening all cirrhotic patients versus only high risk patients versus no screening.

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Table 1 Demographics and Characteristics of Study Subjects, Risk Factors for Varices Study, 1999

	Overall	Patients Without Varices	Patients With Small Varices	Patients with Large/Gastric Varices*
Total number of patients	300	97	109	94
Male/female	206/94	61/36	74/35	71/23
Mean age(in years)	49 (Std Dev ±7.7)	49 (Std Dev ±7.7)	49 (Std Dev ±8.1)	50 (Std Dev ± 7.3)
	N (%)	N (%)	N (%)	N (%)
Etiology of Liver Disease				
Hepatitis C	82 (27)	22 (23)	35 (32)	25 (27)
Hepatitis C/Alcohol	93 (31)	29 (30)	33 (30)	31 (32)
Alcohol	40 (13)	10 (10)	17 (16)	13 (14)
Hepatitis B	15 (5)	7 (7)	1 (1)	7 (8)
Hepatitis B/C	2 (1)	0	1 (1)	1 (1)
PBC/PSC^	31 (10)	18 (16)	9 (8)	4 (4)
Metabolic	3 (1)	1 (1)	1 (1)	1 (1)
Other	19 (7)	7 (7)	5 (5)	7 (8)
Cryptogenic	15 (5)	3 (3)	7 (6)	5 (5)
Medication Use				
Beta-blocker	7 (2)	4 (4)	2 (2)	1 (1)
Long-acting Nitrate	0	0	0	0
Diuretic[#]	194 (65)	52 (54)	72 (66)	70 (74)
Child-Pugh Classification (Score)[$]				
A (5-6)	66 (22)	37 (38)	19 (17)	10 (11)
B (7-9)	174 (58)	45 (46)	62 (57)	67 (71)
C (10-15)	60 (20)	15 (16)	28 (26)	17 (18)

* 4 patients with isolated gastric varices, 9 patients with gastric varices associated with small esophageal varices, 20 patients with gastric varices associated with large varices
^ Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis
[#]p-value=0.01 by Chi-square test
[$]p-value<0.001 by Chi-square test

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

		Overall	Patient Without Varices	Patients With Small Varices	Patients with Large/Gastric Varices*
Total number of patients		300	97	109	94
Physical Exam		N (%)	N (%)	N (%)	N (%)
Ascites#	none	136 (45.3)	55 (57)	48 (44)	33 (35)
	non-tense	149 (49.7)	40 (41)	54 (50)	55 (59)
	tense	15 (5)	2 (2)	7 (6)	6 (6)
Splenomegaly		127 (42.3)	45 (46)	42 (39)	40 (43)
Encephalopathy$	none	165 (55)	64 (66)	58 (53)	43 (46)
	mild	134 (44.7)	33 (34)	50 (46)	51 (54)
	severe	1 (0.3)	0	1 (1)	0
Spider angiomas		186 (62)	59 (61)	64 (59)	63 (67)
Laboratory Data		Mean (Standard deviation)	Mean (Standard deviation)	Mean (Standard deviation)	Mean (Standard deviation)
Total bilirubin(mg/dL)		2.7 (3.1)	3.0 (4.4)	2.7 (2.5)	2.4 (1.6)
AST(U/L)		104.7 (80.0)	95.5 (73.2)	115.9 (86.1)	101.3 (78.7)
ALT(U/L)		82.9 (72.9)	80.1 (75.7)	86.4 (72.2)	81.6 (71.4)
Albumin(g/dL)		3.1 (0.6)	3.2 (0.7)	2.9 (0.6)	3.0 (0.6)
Urea nitrogen(mg/dL)		15.3 (9.2)	16.1 (11.6)	15.3 (8.4)	14.6 (6.9)
Creatinine(mg/dL)		1.07 (0.66)	1.2 (0.9)	1.0 (0.6)	1.0 (0.3)
Platelet count^ ($x1,000/mm^3$)		104.7 (66.5)	128.5 (76.7)	107.8 (70.1)	76.5 (32.2)
Prothrombin time(sec)		14.2 (2.0)	14.1 (2.1)	14.4 92.4)	14.1 (1.4)
Abdominal ultrasound		N (%)	N (%)	N (%)	N (%)
Splenomegaly		195 (65)	60 (62)	66 (61)	69 (73)
Ascites	none	140 (46.7)	54 (56)	51 (47)	35 (37)
	small	141 (47.0)	40 (41)	49 (45)	52 (55)
	large	19 (6.3)	3 (3)	9 (8)	7 (8)

* 4 patients with isolated gastric varices, 9 patients with gastric varices associated with small esophageal varices, 20 patients with gastric varices associated with large varices

#p-value=0.035 by Chi-square test

$p-value=0.043 by Chi-square test

^Two-tailed p-value<0.001 by ANOVA. Tukey HSD post-hoc test revealed that the large/gastric varices group's mean platelet count was significantly different from the other two groups

TABLE 3
Endoscopic Findings of Study Subjects, Risk Factors for Varices Study, 1999

		N (%)
Esophageal Varices	none	97 (32.3)
	small	109 (36.3)
	large	94 (31.3)
Gastric Varices Associated with		
Small Esophageal Varices		9 (3)
Large Esophageal Varices		20 (6.7)
Isolated Gastric Varices		4 (1.3)

TABLE 4
Relationship of Child-Pugh Class and Platelet Count to the Presence of Varices in Study Subjects, Risk Factors for Varices Study, 1999

	Presence of Varices		
	NO	YES	Total
Child-Pugh Class			
A	37 (38.1%)	29 (14.3%)	66
B	45 (46.4%)	129 (63.5%)	174
C	15 (15.5%)	45 (22.2%)	60
Total	97	203	300
Platelet Count			
Less than 90,000/mm^3	36 (37.1%)	125 (61.6%)	161
Greater than 90,000/mm^3	61(62.9%)	78 (38.4%)	139
Total	97	203	300

TABLE 5
Results of Binary Logistic Regression Analysis for the Risk Factors for the Presence of Varices Adjusted for Confounders, Risk Factors for Varices Study, 1999

Variable	Coefficient	Standard Error	Two-sided p-value	Adjusted* Odds Ratio	95% Confidence Interval	Difference Associated with Odds Ratio
Platelet Count	0.8677	0.2649	0.0009	2.4	1.43-4.01	Platelet count $\leq$90,000/mm^3 vs >90,000/mm^3
Child-Pugh Class						
	1.1109	0.3134	0.0001	3.04	1.64-5.61	Child-Pugh Class B vs. A
	1.0082	0.4098	0.0028	2.74	1.23-6.12	Child-Pugh Class C vs. A

*Diuretic Use

TABLE 6
Study Patients Categorized by the Presence of Varices and Child-Pugh Class and Platelet Count, Risk Factors for varices Study, 1999

	Presence of Varices		
Child-Pugh Class and Platelet Count Status	NO	YES	Total
Class A and Platelet Count >90,000/mm^3	26 (65.0%)	14 (35.0%)	26
Class A and Platelet Count <90,000/mm^3	11 (42.3%)	15 (57.7%)	40
Class B and Platelet Count >90,000/mm^3	25 (33.3%)	50 (66.7%)	75
Class B and Platelet Count <90,000/mm^3	20 (20.2%)	79 (79.8%)	99
Class C and Platelet Count >90,000/mm^3	9 (39.1%)	14 (60.9%)	23
Class C and Platelet Count <90,000/mm^3	6 (16.2%)	31 (83.8%)	37
Total	97	203	300

TABLE 7

Relationship of Child-Pugh Class and Platelet Count to the Presence of Large Varices in Study Subjects, Risk Factors for Varices Study, 1999

		Presence of Large Varices		
		NO	YES	Total
Child-Pugh Class				
	A	56 (27.3%)	10 (10.5%)	66
	B	106 (51.7%)	68 (71.6%)	174
	C	43 (21.0%)	17 (17.9%)	60
Total		205	95	300
Platelet Count				
Less than 80,000/mm^3		77 (37.6%)	58 (61.1%)	135
Greater than 80,000/mm^3		128 (62.4%)	37 (38.9%)	165
Total		205	95	300

TABLE 8
Results of Binary Logistic Regression Analysis for the Risk Factors for the Presence of Large Varices, Risk Factors for Varices Study, 1999

Variable	Coefficient	Standard Error	Two-sided p-value	Odds Ratio	95% Confidence Interval	Difference Associated with Odds Ratio
Platelet Count	0.8541	0.2596	0.001	2.3	1.41-3.85	Platelet count $\leq$80,000/mm^3 vs. >80,000/mm^3
Child-Pugh Class	1.0119	0.3757	0.0071	2.75	1.32-5.75	Child-Pugh Class B/C vs. A

TABLE 9
Study Patients Categorized by the Presence of Large Varices and Child-Pugh Class and Platelet Count, Risk Factors for Varices Study, 1999

	Presence of Large Varices		
	NO	YES	
Child-Pugh Class and Platelet Count Status			
Class A and Platelet Count >80,000/mm^3	42 (89.4%)	5 (10.6%)	47
Class A and Platelet Count <80,000/mm^3	14 (73.7%)	5 (26.3%)	19
Class B/C and Platelet Count >80,000/mm^3	86 (72.9%)	32 (27.1%)	118
Class B/C and Platelet Count <80,000/mm^3	63 (54.3%)	53 (45.7%)	116
Total	205	95	300

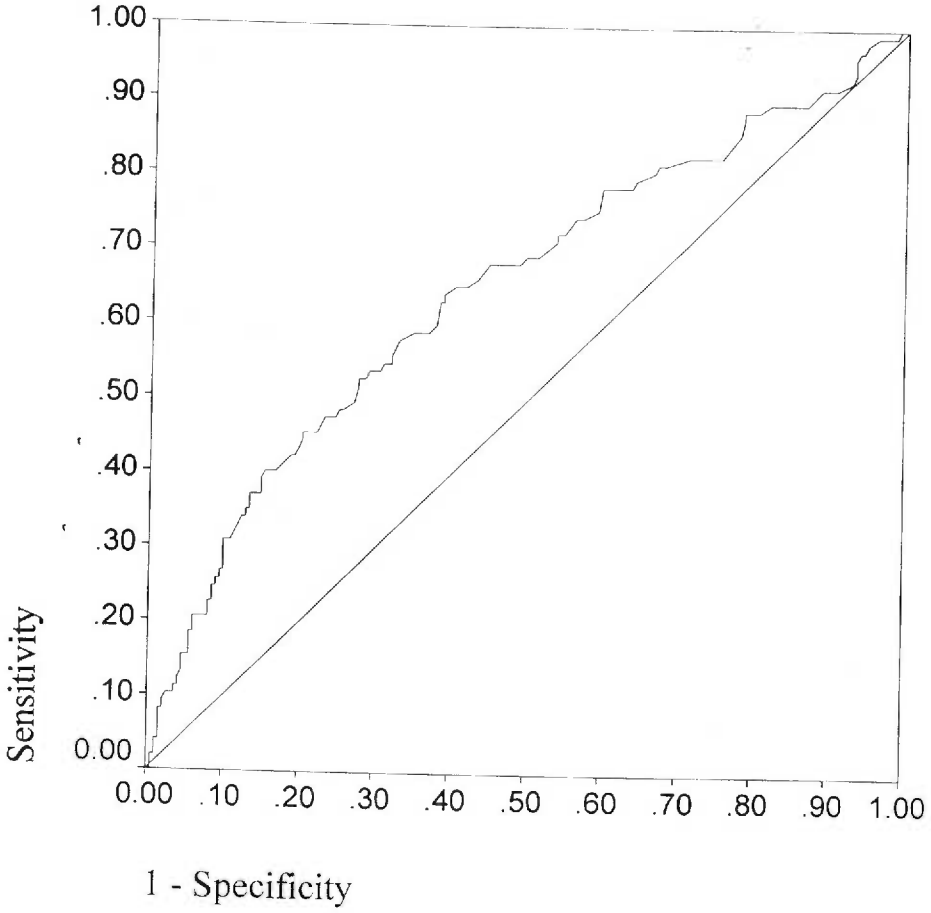

Figure 1
Receiver Operator Characteristic Curve for Platelet Count and the Presence of Varices in 300 Study Subjects, Risk Factors for Varices Study, 1999. Maximum sensitivity (0.598) and minimum 1-specificity (0.379) occurs at a platelet count of 90,000/cubic mm.

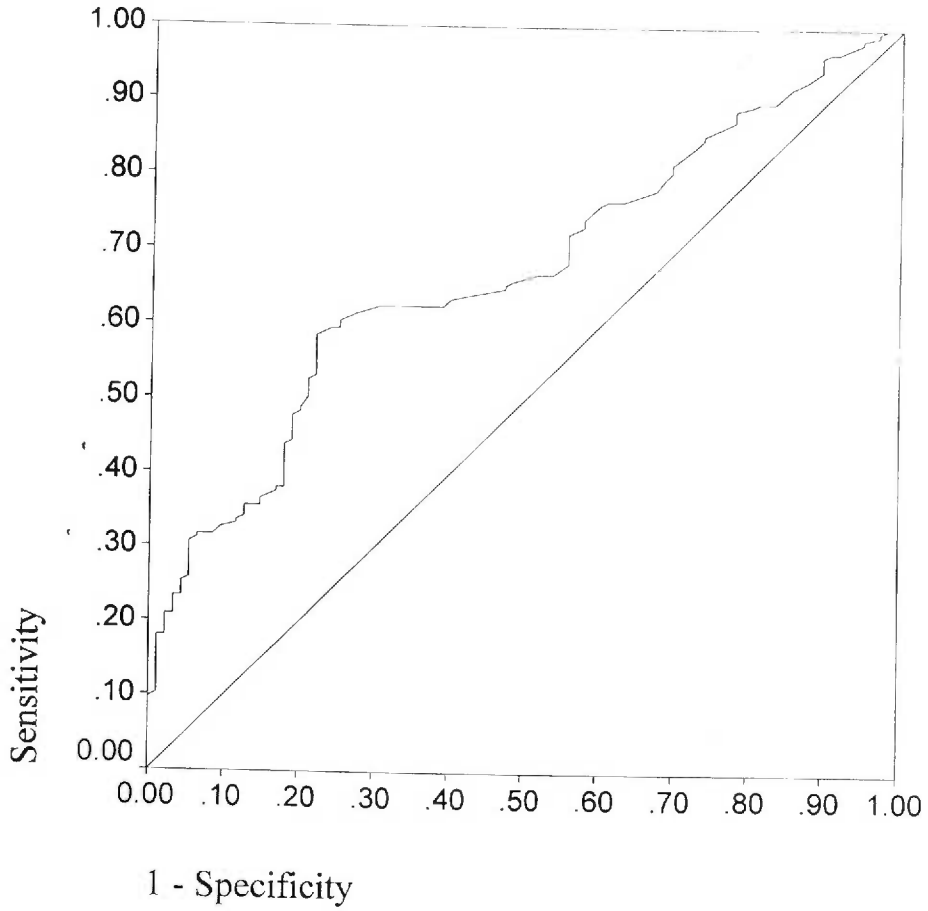

Figure 2
Receiver Operator Characteristic Curve for Platelet Count and the Presence of Large Varices in 300 Study Subjects, Risk Factors for Varices Study, 1999. Maximum sensitivity (0.624) and minimum 1-specificity (0.326) occurs at a platelet count of 80,000/cubic mm.

APPENDIX

Table 1 Child-Turcotte Prognostic Classification (Pugh's Modification)

I. Specific Scores

Factor	Points		
	1	2	3
Encephalopathy (grade)	0	1-2	3-4
Ascites	None	Slight	Moderate
Bilirubin (mg/dL)	1-2	2-3	>3
Albumin (g/dL)	≥3.5	2.8-3.5	<2.8
Prothrombin time (seconds prolonged) Or [INR]	1-4 [<1.7]	5-6 [1.7-2.3]	>6 [.2.3]

II. Summary Scores

Grade	Total Score (points)
A	5-6
B	7-9
C	10-15

TABLE 2: Codebook for Variables in Risk Factors for Varices Study, 1999

Variable Name	Data Type	Comments
Dependent Variables	(case scenarios)	
EVX	0,1	varices present=1, varices not present=0
LGEVX	0,1	large varices/gastric varices present=1, not present=0
OrdVx	0,1,2	large/gastric varices=2, small varices=1, no varices=0
Independent Variables		
Age	continuous	
Gender	nominal	male/female
Etiology	nominal	Hepatitis B=1 Hepatitis C=2 Alcohol=3 Hepatitis B/C=4 Hepatitis C/Alcohol=5 Primary biliary cirrhosis or sclerosing cholangitis=6 Metabolic (Non-alcoholic Steatohepatitis)=7 Other (Hemochromatosis)=8 Cryptogenic=9
Diuretic use	nominal	yes/no
Peascites	ordinal	Presence of ascites on physical exam (none=0, nontense=1, tense ascites=2)
Peascites(cat)	ordinal	Presence of ascites (yes=1, no=0)
Pespider	nominal	Presence of spider angiomata on physical examination (yes=1, no=0)

TABLE 2: Codebook for Variables in Risk Factors for Varices Study, 1999

Variable Name	Data Type	Comments
Pespleen	nominal	Presence of splenomegaly on physical examination (yes=1, no=0)
PSE	ordinal	Presence of hepatic encephalopathy (none=0, mild=1, severe=2)
Albumin	continuous	serum albumin
Albumin2.0	categorical	serum albumin less than 2.0 =0, greater than 2.0 =1
Albumin2.5	categorical	serum albumin less than 2.5 =0, greater than 2.5 =1
Albumin3.0	categorical	serum albumin less than 3.0 =0, greater than 3.0 =1
PT	continuous	Serum prothrombin time
PT13	categorical	Serum prothrombin time less than 13 =0, greater than 13 =1
Tbili	continuous	Serum total bilirubin
Tbili1.5	categorical	Serum total bilirubin less than 1.5 =0, greater than 1.5 =1
Tbili2.0	categorical	Serum total bilirubin less than 2.0 =0, greater than 2.0 =1
Tbili3.0	categorical	Serum total bilirubin less than 3.0 =0, greater than 3.0 =1
LNBILI	continuous	Natural log transformation of sern total bilirubin
BUN	continuous	Serum blood urea nitrogen
LNBUN	continuous	Natural log transformation of serum blood urea nitrogen
CR	continuous	Serum creatinine
LNCR	continuous	Natural log transformation of serum creatinine
CR1.0	categorical	Serum creatinine less than 1.0 =0, greater than 1.0 =1
CR1.5	categorical	Serum creatinine less than 1.5 =0, greater than 1.5 =1
CR2.0	categorical	Serum creatinine less than 2.0 =0, greater than 2.0 =1

TABLE 2: Codebook for Variables in Risk Factors for Varices Study, 1999

Variable Name	Data Type	Comments
AST	continuous	Serum aspartate aminotransferase
LNAST	continuous	Natural log transformation of AST
AST100	categorical	AST level less than 100 =0, greater than 100 =1
ALT	continuous	Serum alanine aminotransferase
LNALT	continuous	Natural log transformation of ALT
ALT75	categorical	ALT level less than 75 =0, greater than 75 =1
Platelet	continuous	serum platelet count
LNplatelet	continuous	Natural log transformation of serun platelet count
USspleen	nominal	Enlarged spleen=1, normal sized spleen=0 by ultrasound
USascites	ordinal	By ultrasound: no ascites=0, small amount=1, large amount=2
USascites(cat)	categorical	By ultrasound: ascites present=1, not present=0
Child-Pugh Score	ordinal	See Table 1
Child-Pugh Class	ordinal	See Table 1

Table 3
Univariate Logistic Regression Analysis for the Presence of Varices in Risk Factors for Varices Study, 1999

Variable	B	S.E.	Wald	df	Sig	R	Odds Ratio	95% CI for OR Lower	Upper
AGE	.0098	.0161	.3687	1	.5437	.0000	1.0098	.9785	1.0421
GENDER(1)	-.3889	.2614	2.2145	1	.1367	-.0238	.6778	.4061	1.1312
ETIOLOGY			13.3321	8	.1009	.0000			
ETIOLOGY(1)	.8698	.5744	2.2926	1	.1300	.0278	2.3864	.7741	7.3570
ETIOLOGY(2)	.9651	.6334	2.3215	1	.1276	.0292	2.6250	.7585	9.0840
ETIOLOGY(3)	6.0662	15.7342	.1486	1	.6998	.0000	431.0201	.0000	1.065E+16
ETIOLOGY(4)	.6581	.5639	1.3619	1	.2432	.0000	1.9310	.6395	5.8313
ETIOLOGY(5)	-.4590	.6327	.5262	1	.4682	.0000	.6319	.1829	2.1840
ETIOLOGY(6)	.5596	1.3296	.1771	1	.6738	.0000	1.7500	.1292	23.7029
ETIOLOGY(7)	.4055	.7029	.3328	1	.5640	.0000	1.5000	.3783	5.9482
ETIOLOGY(8)	1.2528	.8274	2.2927	1	.1300	.0278	3.5000	.6915	17.7140
DIURETIC(1)	-.7004	.2547	7.5594	1	.0060	-.1213	.4964	.3013	.8178
PEASCITE			8.2556	2	.0161	.1062			
PEASCITE(1)	.6154	.2544	5.8524	1	.0156	.1010	1.8503	1.1239	3.0462
PEASCITE(2)	1.4838	.7791	3.6267	1	.0569	.0656	4.4097	.9576	20.3057
PEASCTYN(1)	.6792	.2501	7.3778	1	.0066	.1193	1.9724	1.2082	3.2199
PESPIDER(1)	-.0735	.2536	.0840	1	.7719	.0000	.9291	.5653	1.5273
PESPLEEN(1)	.2445	.2488	.9655	1	.3258	.0000	1.2770	.7841	2.0796
PSE			6.7851	2	.0336	.0859			
PSE(1)	.6624	.2564	6.6749	1	.0098	.1113	1.9394	1.1734	3.2055
PSE(2)	4.7379	13.4998	.1232	1	.7256	.0000	114.1941	.0000	3.537E+13
PSEYN(1)	.6722	.2562	6.8851	1	.0087	.1137	1.9586	1.1854	3.2360
ALBUMIN	-.6408	.2108	9.2425	1	.0024	-.1385	.5269	.3486	.7964
PT	.0469	.0632	.5509	1	.4579	.0000	1.0480	.9259	1.1862
PT13(1)	.7475	.3028	6.0962	1	.0135	.1042	2.1117	1.1666	3.8225
TBILI	-.0495	.0381	1.6850	1	.1943	.0000	.9517	.8831	1.0256
LNBILI	.1775	.1632	1.1840	1	.2765	.0000	1.1943	.8674	1.6444
TBILI1.5(1)	.5753	.2558	5.0584	1	.0245	.0900	1.7776	1.0768	2.9348
BUN	-.0125	.0130	.9150	1	.3388	.0000	.9876	.9627	1.0132

Table 3 (continued)
Univariate Logistic Regression Analysis for the Presence of Varices in Risk Factors for Varices Study, 1999

Variable	B	S.E.	Wald	df	Sig	R	Odds Ratio	95% CI for OR Lower	Upper
LNBUN	-.0584	.2616	.0498	1	.8234	.0000	.9433	.5650	1.5750
CR	-.4372	.2071	4.4564	1	.0348	-.0807	.6458	.4304	.9692
LNCR	-.7918	.3434	5.3176	1	.0211	-.0937	.4530	.2311	.8880
CR1.0(1)	-.3094	.2476	1.5624	1	.2113	.0000	.7339	.4517	1.1922
CR1.5(1)	-.6625	.4010	2.7295	1	.0985	-.0440	.5155	.2349	1.1314
CR2.0(1)	-1.1249	.5992	3.5248	1	.0605	-.0635	.3247	.1003	1.0507
AST	.0024	.0017	1.8728	1	.1712	.0000	1.0024	.9990	1.0058
LNAST	.3627	.2021	3.2226	1	.0726	.0569	1.4372	.9672	2.1356
AST100	.4631	.2639	3.0797	1	.0793	.0535	1.5891	.9473	2.6655
ALT	.0008	.0018	.2095	1	.6472	.0000	1.0008	.9974	1.0043
LNALT	.1902	.1786	1.1332	1	.2871	.0000	1.2094	.8522	1.7165
ALT75(1)	.3197	.2532	1.5949	1	.2066	.0000	1.3767	.8382	2.2612
PLATELET	-.0078	.0020	15.9734	1	.0001	-.1924	.9922	.9884	.9960
LNPLT	-1.0175	.2439	17.4058	1	.0000	-.2020	.3615	.2241	.5830
CPS	.2419	.0765	9.9888	1	.0016	.1455	1.2737	1.0963	1.4799
CPC			20.4103	2	.0000	.2085			
CPC(1)	1.2968	.3025	18.3815	1	.0000	.2083	3.6575	2.0217	6.6166
CPC(2)	1.3422	.3878	11.9788	1	.0005	.1626	3.8276	1.7899	8.1852
USSPLENO(1)	-.2023	.2565	.6221	1	.4303	.0000	.8168	.4940	1.3505
USASCITE			5.6676	2	.0588	.0665			
USASCITE(1)	.4609	.2550	3.2654	1	.0708	.0579	1.5855	.9618	2.6137
USASCITE(2)	1.2084	.6526	3.4283	1	.0641	.0615	3.3480	.9317	12.0308
USACITYN(1)	.5356	.2489	4.6309	1	.0314	.0835	1.7085	1.0489	2.7827

Table 4
Multivariate Logistic Regression Analysis for the Presence of Varices in Risk Factors for Varices Study, 1999

Model 1

Variable	B	S.E.	Wald	df	Sig	R	Odds Ratio	95% CI for OR Lower	Upper
PLATELET	-.0070	.0020	12.5903	1	.0004	-.1675	.9930	.9891	.9969
CPC			16.4462	2	.0003	.1815			
CPC (1)	1.1981	.3098	14.9553	1	.0001	.1852	3.3139	1.8056	6.0823
CPC (2)	1.2219	.3988	9.3893	1	.0022	.1399	3.3938	1.5532	7.4153
Constant	.5987	.3421	3.0631	1	.0801				

Hosmer and Lemeshow Goodness-of-Fit Test

Chi-square	df	Significance
6.2900	8	.6148

Model 2

Variable	B	S.E.	Wald	df	Sig	R	Odds Ratio	95% CI for OR Lower	Upper
PEASCT (cat)	.6670	.2582	6.6737	1	.0098	.1113	1.9484	1.1746	3.2318
LNPLT	-1.0153	.2486	16.6750	1	.0000	-.1971	.3623	.2226	.5898
Constant	5.0046	1.1482	18.9974	1	.0000				

Hosmer and Lemeshow Goodness-of-Fit Test

Chi-square	df	Significance
9.1128	8	.3329

Table 4 (continued)
Multivariate Logistic Regression Analysis for the Presence of Varices in Risk Factors for Varices Study, 1999

Model 3

Variable	B	S.E.	Wald	df	Sig	R	Odds Ratio	95% CI for OR Lower	Upper
PEASCT (cat)	.5827	.2626	4.9225	1	.0265	.0880	1.7908	1.0703	2.9963
LNPLT	-.9411	.2506	14.1056	1	.0002	-.1790	.3902	.2388	.6376
ALBUMIN	-.4427	.2184	4.1086	1	.0427	-.0747	.6423	.4186	.9855
Constant	6.0862	1.2798	22.6162	1	.0000				

Hosmer and Lemeshow Goodness-of-Fit Test

Chi-square	df	Significance
11.9739	8	.1524

Table 5
Univariate Logistic Regression Analysis for the Presence of Large Varices in Risk Factors for Varices Study, 1999

Variable	B	S.E.	Wald	df	Sig	R	Odds Ratio	95% CI for OR Lower	Upper
AGE	.0232	.0163	2.0371	1	.1535	.0099	1.0235	.9914	1.0567
GENDER(1)	.4278	.2783	2.3637	1	.1242	.0312	1.5339	.8891	2.6466
ETIOLOGY			5.4607	8	.7074	.0000			
ETIOLOGY(1)	-.6906	.5704	1.4659	1	.2260	.0000	.5013	.1639	1.5333
ETIOLOGY(2)	-.5974	.6179	.9346	1	.3337	.0000	.5503	.1639	1.8473
ETIOLOGY(3)	.1335	1.5059	.0079	1	.9293	.0000	1.1429	.0597	21.8701
ETIOLOGY(4)	-.5596	.5624	.9903	1	.3197	.0000	.5714	.1898	1.7204
ETIOLOGY(5)	-1.5149	.7115	4.5330	1	.0332	-.0822	.2198	.0545	.8866
ETIOLOGY(6)	-.5596	1.3296	.1771	1	.6738	.0000	.5714	.0422	7.7397
ETIOLOGY(7)	-.4055	.7029	.3328	1	.5640	.0000	.6667	.1681	2.6437
ETIOLOGY(8)	-.5596	.7536	.5515	1	.4577	.0000	.5714	.1305	2.5026
DIURETIC(1)	.6792	.2758	6.0630	1	.0138	.1041	1.9722	1.1486	3.3863
PEASCITE			6.2538	2	.0439	.0776			
PEASCITE(1)	.6310	.2620	5.8017	1	.0160	.1007	1.8794	1.1247	3.1406
PEASCITE(2)	.7328	.5637	1.6896	1	.1937	.0000	2.0808	.6893	6.2817
PEASCTYN(1)	.6404	.2568	6.2187	1	.0126	.1061	1.8972	1.1469	3.1383
PESPIDER(1)	.2719	.2597	1.0964	1	.2951	.0000	1.3125	.7889	2.1835
PESPLEEN(1)	.0137	.2513	.0030	1	.9566	.0000	1.0138	.6195	1.6590
PSE			5.5948	2	.0610	.0652			
PSE(1)	.5873	.2508	5.4864	1	.0192	.0965	1.7992	1.1006	2.9412
PSE(2)	-4.1513	13.5000	.0946	1	.7585	.0000	.0157	.0000	4.879E+09
PSEYN(1)	.5752	.2505	5.2746	1	.0216	.0935	1.7775	1.0880	2.9041
ALBUMIN	-.0725	.2034	.1270	1	.7216	.0000	.9301	.6243	1.3857
PT	-.0436	.0633	.4730	1	.4916	.0000	.9574	.8456	1.0839
TBILI	-.0545	.0483	1.2712	1	.2595	.0000	.9470	.8614	1.0410
LNBILI	.0890	.1612	.3044	1	.5811	.0000	1.0930	.7969	1.4992
BUN	-.0129	.0148	.7577	1	.3841	.0000	.9872	.9590	1.0162
LNBUN	-.0888	.2649	.1124	1	.7374	.0000	.9150	.5444	1.5378
CR	-.4505	.3005	2.2485	1	.1337	-.0258	.6373	.3537	1.1484

Table 5 (continued)
Univariate Logistic Regression Analysis for the Presence of Large Varices in Risk Factors for Varices Study, 1999

Variable	B	S.E.	Wald	df	Sig	R	Odds Ratio	95% CI for OR Lower	Upper
LNCR	-.5943	.3835	2.4020	1	.1212	-.0328	.5519	.2603	1.1703
CR1.0(1)	-.2501	.2504	.9976	1	.3179	.0000	.7787	.4766	1.2721
CR1.5(1)	-.1618	.4381	.1365	1	.7118	.0000	.8506	.3604	2.0072
CR2.0(1)	-.8689	.7847	1.2259	1	.2682	.0000	.4194	.0901	1.9526
AST	-.0008	.0016	.2524	1	.6154	.0000	.9992	.9960	1.0023
ALT	-.0003	.0017	.0350	1	.8517	.0000	.9997	.9963	1.0031
PLATELET	-.0155	.0034	20.6776	1	.0000	-.2233	.9846	.9780	.9912
LNPLT	-1.3408	.2781	23.2406	1	.0000	-.2381	.2616	.1517	.4513
CPS	.0550	.0702	.6139	1	.4333	.0000	1.0565	.9208	1.2122
CPC			12.2097	2	.0022	.1480			
CPC(1)	1.2785	.3768	11.5133	1	.0007	.1594	3.5912	1.7160	7.5155
CPC(2)	.7944	.4471	3.1570	1	.0756	.0556	2.2132	.9214	5.3161
USSPLENO(1)	-.5833	.2735	4.5500	1	.0329	-.0825	.5580	.3265	.9538
USASCITE			5.5359	2	.0628	.0640			
USASCITE(1)	.5612	.2618	4.5939	1	.0321	.0832	1.7528	1.0492	2.9283
USASCITE(2)	.7802	.5040	2.3962	1	.1216	.0325	2.1818	.8125	5.8589
USACITYN(1)	.5878	.2545	5.3348	1	.0209	.0944	1.8000	1.0931	2.9641

Table 6
Multivariate Logistic Regression Analysis for the Presence of Large Varices in Risk Factors for Varices Study, 1999

Model 1

Variable	B	S.E.	Wald	df	Sig	R	Odds Ratio	95% CI for OR Lower	Upper
PLATELET	-.0146	.0034	18.2029	1	.0000	-.2080	.9855	.9790	.9922
CPC			8.9958	2	.0111	.1155			
CPC (1)	1.0763	.3897	7.6299	1	.0057	.1226	2.9339	1.3670	6.2970
CPC (2)	.5029	.4639	1.1756	1	.2783	.0000	1.6536	.6662	4.1046
Constant	-.1900	.4733	.1611	1	.6882				

Hosmer and Lemeshow Goodness-of-Fit Test

Chi-square	df	Significance
10.1802	8	.2526

Model 2

Variable	B	S.E.	Wald	df	Sig	R	Odds Ratio	95% CI for OR Lower	Upper
PEASCT (cat)	.6676	.3030	4.9993	1	.0254	.0895	1.9691	1.0872	3.5663
CPC			8.5246	2	.0141	.1099			
CPC (1)	.8274	.4072	4.1285	1	.0422	.0754	2.2874	1.0297	5.0814
CPC (2)	.0048	.5154	.0001	1	.9926	.0000	1.0048	.3659	2.7591
PLATELET	-.0152	.0035	19.1254	1	.0000	-.2138	.9849	.9782	.9916
Constant	5.0046	1.1482	18.9974	1	.0000				

Hosmer and Lemeshow Goodness-of-Fit Test

Chi-square	df	Significance
14.1082	8	.0790

Table 6 (continued)
Multivariate Logistic Regression Analysis for the Presence of Large Varices in Risk Factors for Varices Study, 1999

Model 3

Variable	B	S.E.	Wald	df	Sig	R	Odds Ratio	95% CI for OR Lower	Upper
DIURETIC (1)	.6209	.3005	4.2703	1	.0388	.0779	1.8607	1.0325	3.3531
LNPLT	-1.2561	.2861	19.2775	1	.0000	-.2148	.2848	.1625	.4989
CPC			8.9590	2	.0113	.1151			
CPC (1)	.9806	.3915	6.2748	1	.0122	.1068	2.6660	1.2378	5.7421
CPC (2)	.2626	.4771	.3031	1	.5820	.0000	1.3004	.5105	3.3125
Constant	3.7053	1.3403	7.6428	1	.0057				

Hosmer and Lemeshow Goodness-of-Fit Test

Chi-square	df	Significance
10.9354	8	.2054

Table 7
Multivariate Ordinal Logistic Regression Analysis for the Presence of Large Varices in Risk Factors for Varices Study, 1999

Final Ordinal Logistic Model

Variable	B	S.E.	Wald	df	Sig
PLATELET	.0088	.0019	21.1609	1	.0000
CPC			18.2259	2	.0001
CPC (1)	-1.2303	.2883	18.2259	1	.0000
CPC (2)	.2783	.2810	.9800	1	.3221
Constant1	-.8518	.3295	6.6800	1	.0097
Constant2	.8780	.3305	7.0600	1	.0079

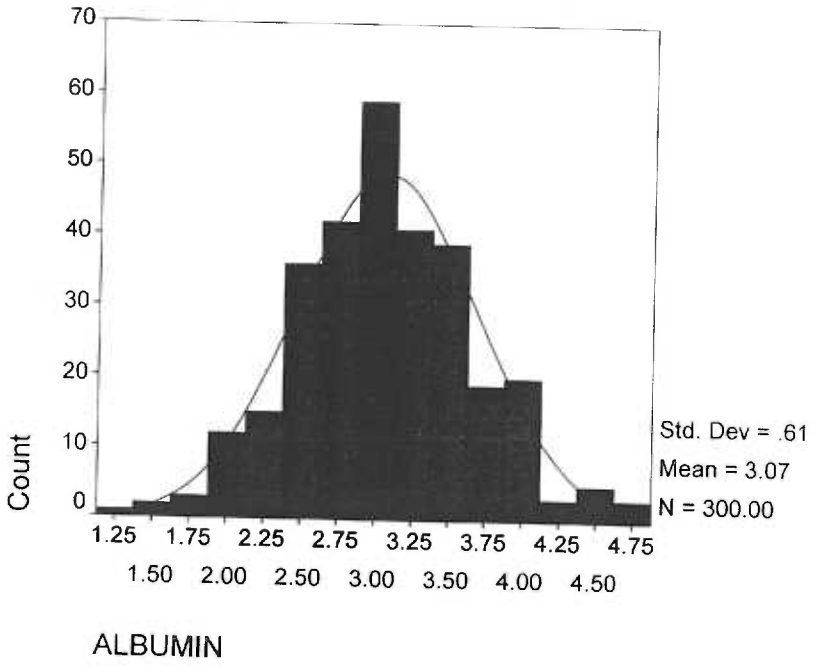

Figure 1 Histogram of Serum Albumin of Study Subjects, Risk Factors for Varices Study, 1999

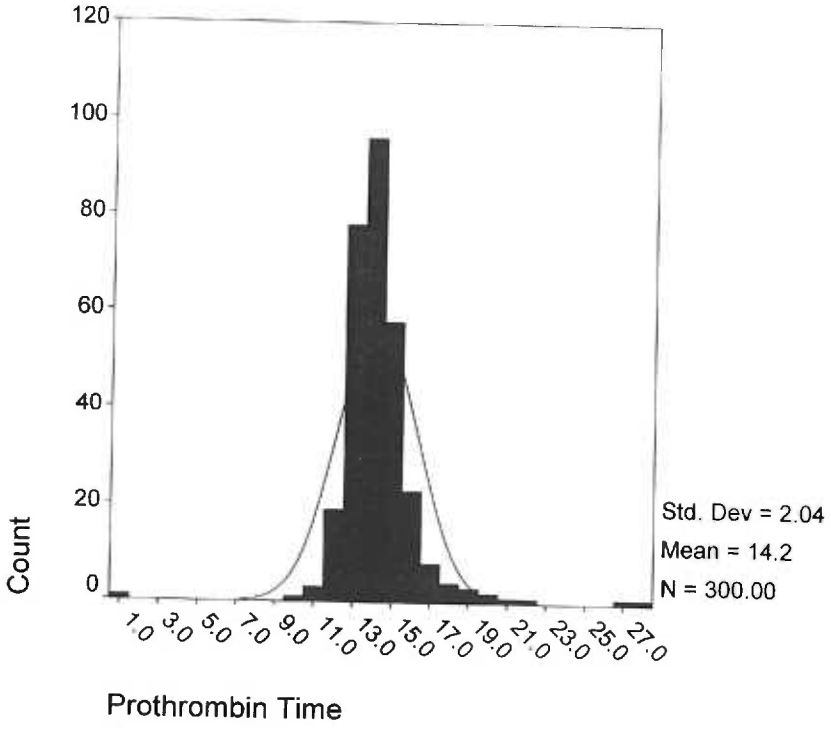

Figure 2 Histogram of Prothrombin Time of Study Subjects, Risk Factors for Varices Study, 1999

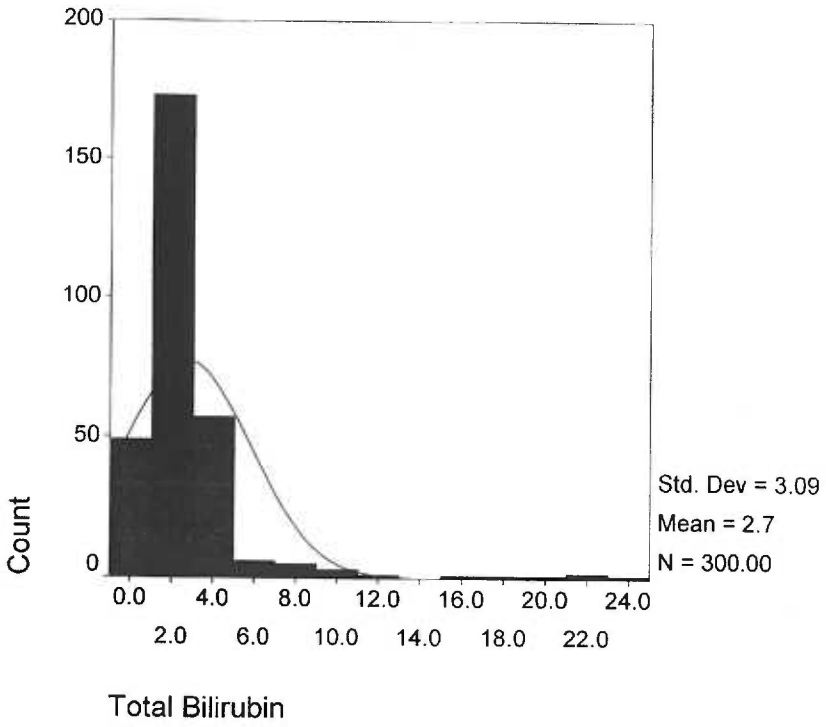

Figure 3 Histogram of Total Bilirubin of Study Subjects, Risk Factors for Varices Study, 1999

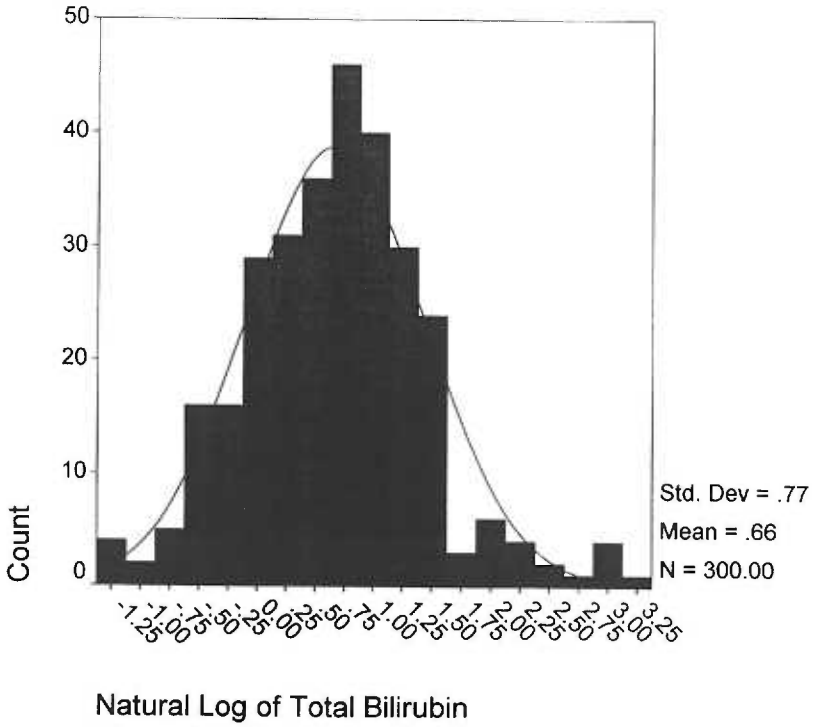

Figure 4 Histogram of the Natural Log of Total Bilirubin of Study Subjects, Risk Factors for Varices Study, 1999

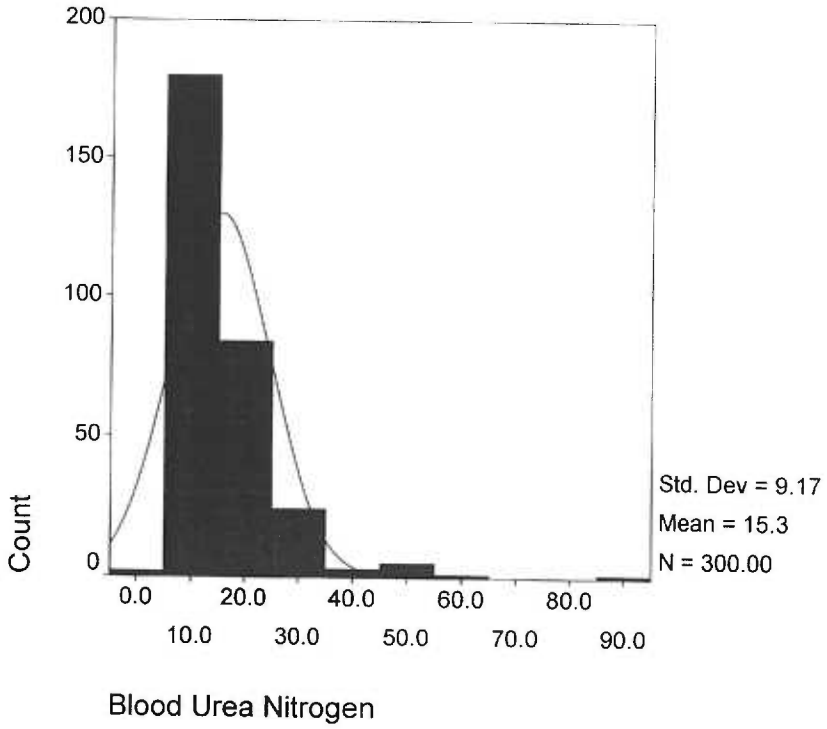

Figure 5 Histogram of Blood Urea Nitrogen of Study Subjects, Risk Factors for Varices Study, 1999

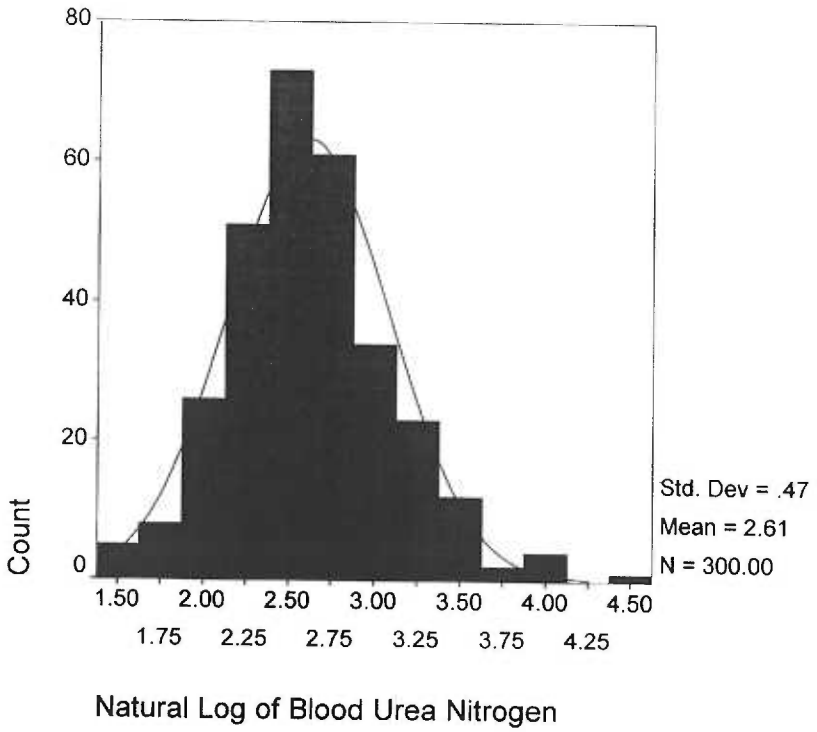

Figure 6 Histogram of the Log Transformation of Blood Urea Nitrogen of Study Subjects, Risk Factors for Varices Study, 1999

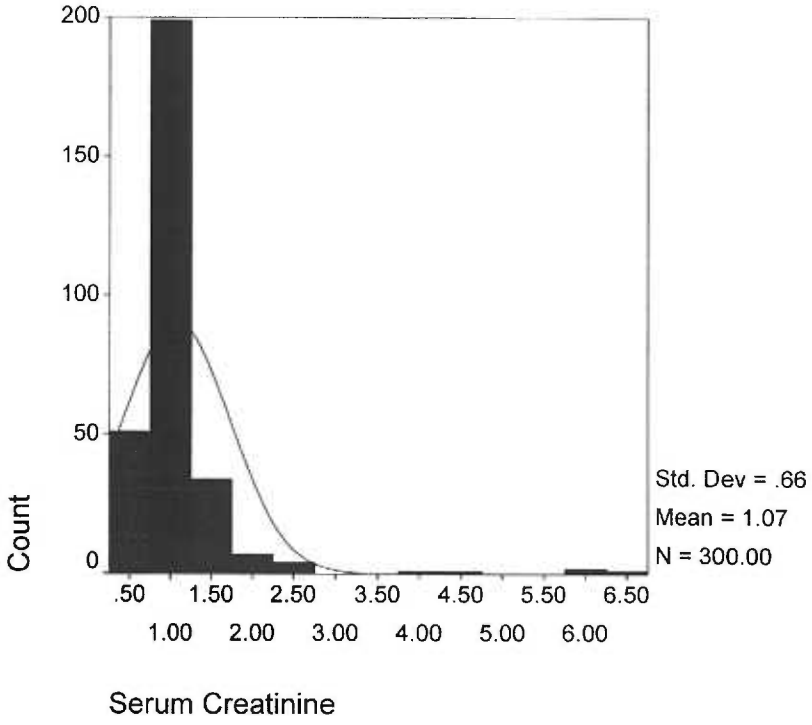

Figure 7 Histogram of Serum Creatinine of Study Subjects, Risk Factors for Varices Study, 1999

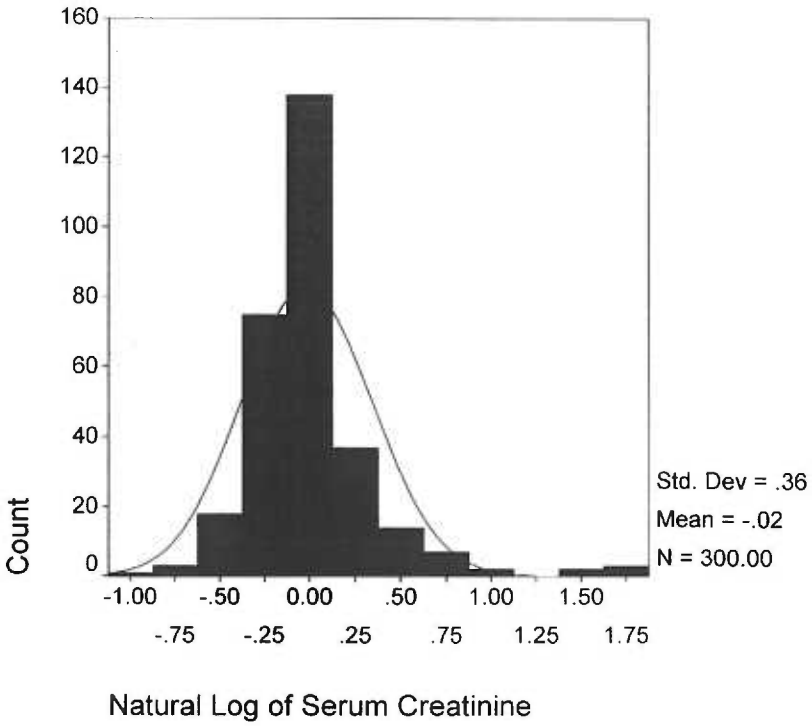

Figure 8 Histogram of the Natural Log of Serum Creatinine of Study Subjects, Risk Factors for Varices Study, 1999

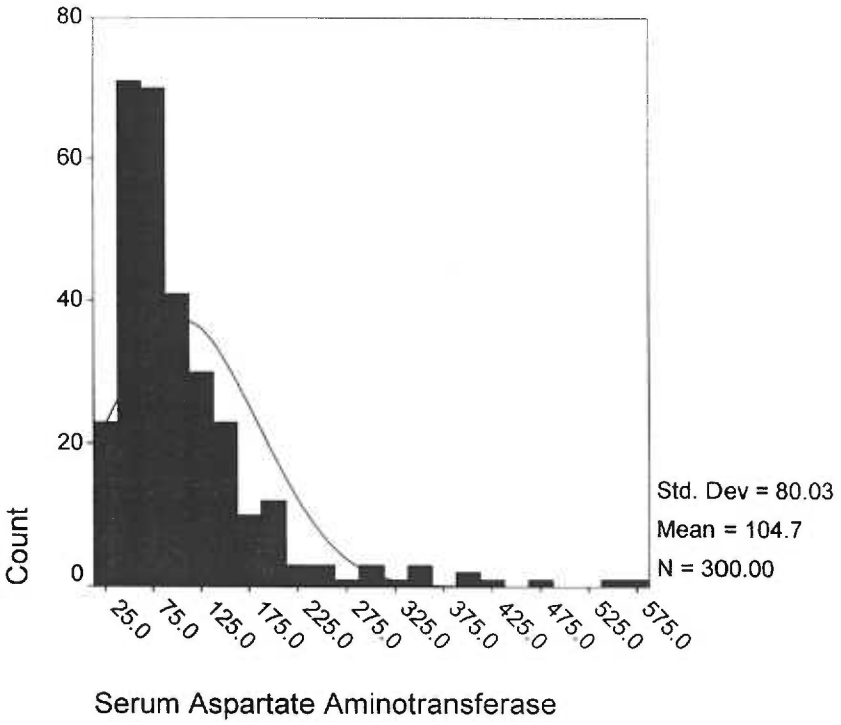

Figure 9 Histogram of Serum Aspartate Aminotransferase of Study Subjects, Risk Factors for Varices Study, 1999

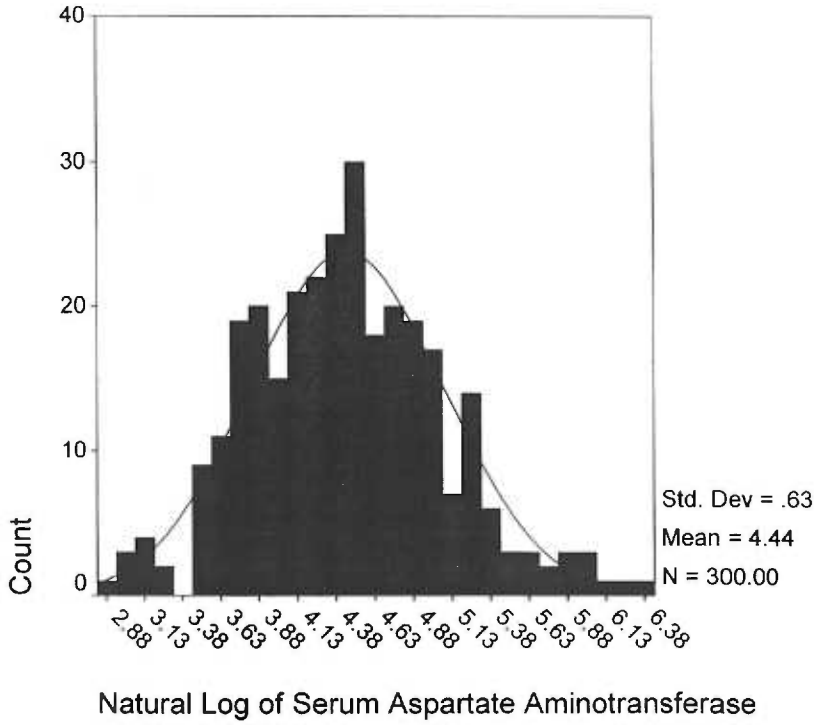

Figure 10 Histogram of Natural Log of Serum Aspartate Aminotransferase of Study Subjects, Risk Factors for Varices Study, 1999

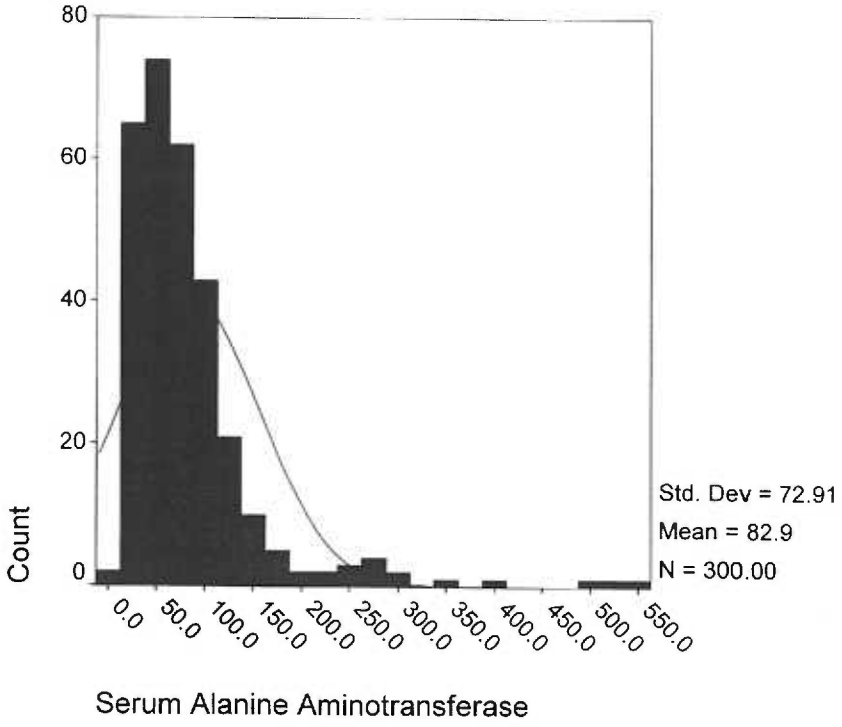

Figure 11 Histogram of Serum Alanine Aminotransferase of Study Subjects, Risk Factors for Varices Study, 1999

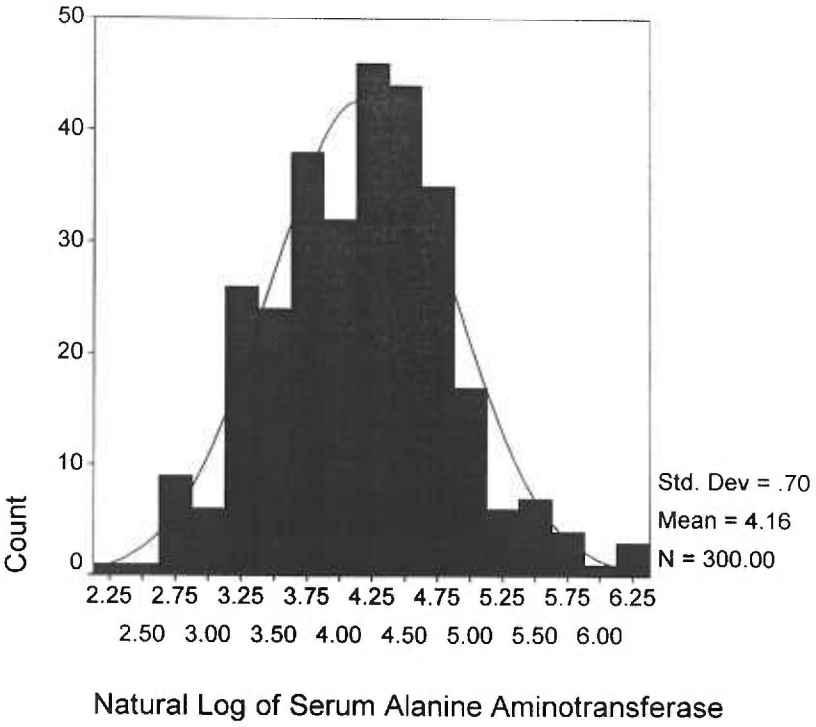

Figure 12 Histogram of the Natural Log of Serum Alanine Aminotransferase of Study Subjects, Risk Factors for Varices Study, 1999

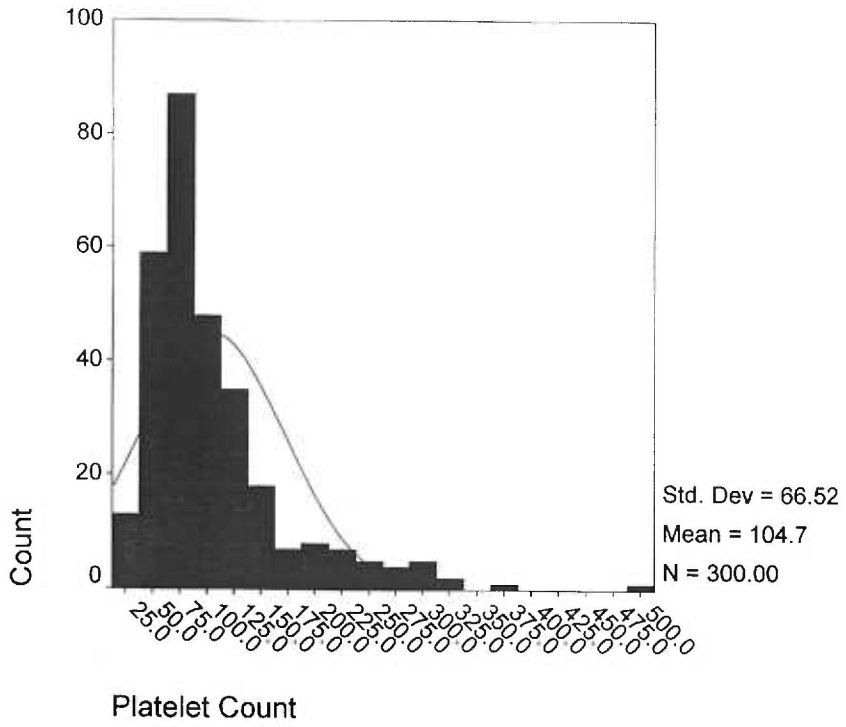

Figure 13 Histogram of Platelet Count of Study Subjects, Risk Factors for Varices Study, 1999

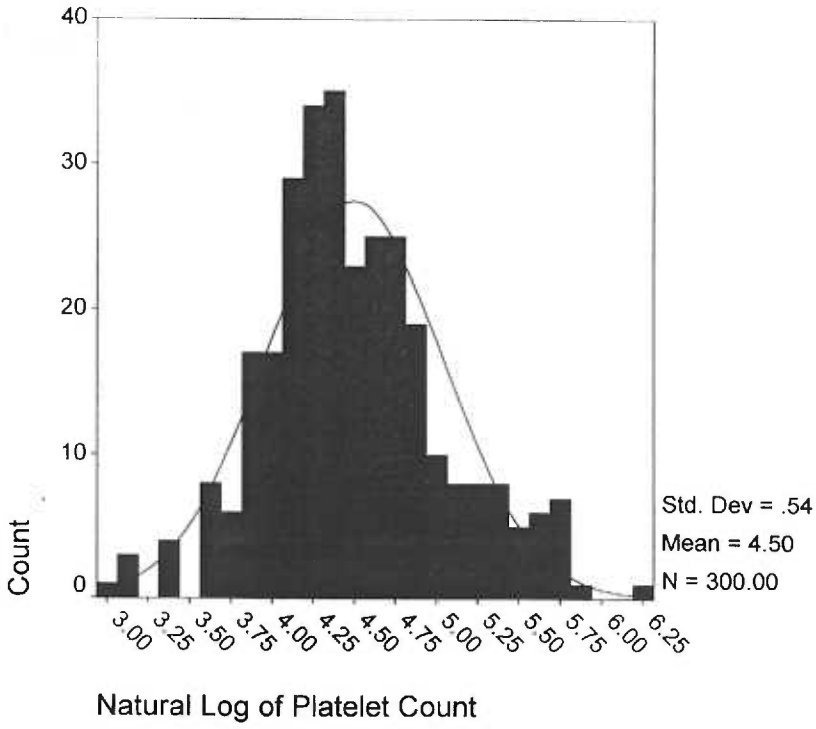

Figure 14 Histogram of the Natural Log of Platelet Count of Study Subjects, Risk Factors for Varices Study, 1999