Noninvasive predictors of large varices in patients hospitalized with gastroesophageal variceal hemorrhage

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Received: 9 June 2007 / Accepted: 7 September 2007 / Published online: 14 December 2007
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Abstract

Aim To identify noninvasive factors predicting the presence of large varices (LV) in patients hospitalized with gastroesophageal variceal hemorrhage (GEVH).

Methods Case records of patients admitted with GEVH between January 1998 and June 2005 were retrospectively analyzed. Relevant clinical parameters assessed included Child-Pugh class, ascites (clinical and/or on ultrasound), portosystemic encephalopathy (PSE), splenomegaly (clinical and/or on ultrasound), and hemodynamic instability. The laboratory parameters assessed were hemoglobin level, platelet count, prothrombin time, serum bilirubin, and albumin. The ultrasonographic characteristics noted were splenic size, presence of splenic varices, and portal vein diameter.

Results A total of 420 patients (264 men) presented with GEVH during the study period. The mean age, gender distribution, and presence of cirrhosis were similar in the two groups. Liver cirrhosis with hepatocellular carcinoma (HCC), Child-Pugh class C, presence of clinically detectable ascites, grade 3–4 PSE, detectable splenomegaly, previous history of GEVH, hemodynamic instability and platelet count <91,000 were more common in the LV group. The frequency of radiologically detected ascites, splenomegaly, and portal vein diameter were similar in both groups. On multivariate analysis, the independent predictors for the presence of LV were cirrhosis with HCC,

clinically detectable splenomegaly, hemodynamic instability, a previous history of GEVH, platelet count <91,000, and splenic size ≥ 158 mm.

Conclusion Cirrhosis with HCC, clinical splenomegaly, hemodynamic instability, a previous history of GEVH, thrombocytopenia (i.e., platelet count <91,000), and splenic size ≥ 158 mm are independent noninvasive predictors of large varices in patients hospitalized with gastroesophageal variceal hemorrhage.

Keywords Gastroesophageal variceal hemorrhage · Predictors · Varices

Introduction

Portal hypertension commonly accompanies the presence of liver cirrhosis, and the development of esophageal varices (EV) is one of the major complications of portal hypertension [1]. The prevalence of EV in patients with liver cirrhosis may range from 60% to 80%, and the reported mortality from variceal bleeding ranges from 17% to 57% [2–4]. Large EVs (LVs) are more likely to bleed than small EVs (SVs) [5].

The American Association for the Study of Liver Disease and the Baveno IV Consensus Conference on portal hypertension recommended that all cirrhotic patients should be screened for the presence of EV when liver cirrhosis is diagnosed [6, 7]. Investigators have attempted to identify characteristics that noninvasively predict the presence of varices. These studies have shown that biochemical, clinical, and ultrasonographic parameters alone or together have good predictive power for noninvasively assessing the presence of EV [8–24]. Overall, the most common result of these studies was that parameters such as

Communicated by Shiv Kumar Sarin, M.D.

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splenomegaly, thrombocytopenia, Childs score, ascites, portal flow patterns, and platelet count—splenic size ratio were predictors of the presence of EV.

However, most of these studies were done in patients with compensated cirrhosis. There is insufficient data regarding the decompensated patient presenting with a GEVH, where all these variables may differ widely. Furthermore, patients with LV bleed more profusely than those with SV, and comparatively may need more aggressive management [5]. The knowledge that a patient may be suffering from LV would be beneficial to the endoscopist as well in preparing a strategy for therapeutic intervention.

We therefore sought to identify variables that would aid in identifying patients with GEVH due to large varices, and may help to triage this subgroup for aggressive resuscitative measures, and early therapeutic endoscopy.

Methods

Case records of patients admitted to our hospital with GEVH due to cirrhosis of the liver between January 1998 and June 2005 were analyzed retrospectively. In our hospital, all patients with GEVH are admitted to a dedicated Gastrointestinal Bleeding Control Unit, which is an intensive care area equipped with hemodynamic monitors, pulse oxymeters, trained nurses and physicians, and a 24-h endoscopy service. Splanchnic vasoconstrictors like terlipressin and octreotide are regularly used, when indicated. Sengstaken–Blakemore tube is used for emergency hemostasis in patients with exsanguinating and uncontrollable upper GI hemorrhage.

Variceal band ligation is the treatment modality of choice, except when visibility is poor owing to torrential bleed, in which case ethanolamine oleate sclerotherapy is performed. Patients with a GEVH undergo endoscopy as soon as possible, preferably within 12 h, after adequate resuscitation as per hospital policy.

The relationship of various clinical and laboratory parameters at admission to the presence of LV was assessed. The clinical parameters were age, gender, diagnosis (cirrhosis alone, cirrhosis with hepatocellular carcinoma [HCC], cirrhosis with portal vein thrombosis [PVT], cirrhosis with HCC and PVT), Child-Pugh class, presence of clinically detectable ascites, presence of portosystemic encephalopathy (PSE) according to the West Haven criteria [25], detectable splenomegaly, a previous history of GEVH, and hemodynamic instability.

The laboratory parameters assessed were hemoglobin, platelet count, prothrombin time, serum bilirubin, and albumin. All laboratory parameters were acquired pre-endoscopy. The ultrasonographic characteristics noted were bipolar splenic diameter, any degree of ascites, and portal

vein diameter. The spleen was considered enlarged if the bipolar diameter exceeded 130 mm, while the portal vein was considered enlarged if its diameter exceeded 11 mm [15].

A diagnosis of cirrhosis was on the basis of biochemical parameters and imaging studies and/or liver biopsy, where available. HCC was classified as unifocal (1 lesion) or multifocal (>1 lesion) and was diagnosed when two of the following three were present: a space-occupying lesion on ultrasonography and/or CT scan, liver biopsy, or raised serum α -fetoprotein level. PVT was diagnosed on ultrasound Doppler scanning or CT. It was defined as complete if the main PV was thrombosed, or partial if either of its branches were involved, with the main PV being patent. Ascites was graded as clinically detectable or only ultrasonographically detectable. PSE was categorized as absent, stage 1–2, or stage 3–4.

Hemodynamic instability was defined as a systolic blood pressure <100 mm Hg, a postural change of >20 mm Hg, and/or pulse rate >100/min [7]. Each patient had a complete biochemical and clinical examination. All patients were classified according to Child-Pugh's criteria. All patients underwent upper digestive endoscopy and ultrasonography of the abdomen to evaluate the presence of signs of portal hypertension (presence and degree of EV, splenomegaly, and ascites). All endoscopies were performed in a single endoscopy unit using a video endoscope, and all EV were classified according to size. Small EV were defined as varices that flatten with insufflation or minimally protrude into the esophageal lumen, while large EV were defined as varices that protrude into the esophageal lumen and touch each other (presence of confluence), or that fill at least 50% of the esophageal lumen [26]. Patients with isolated gastric varices, and those who had undergone any endoscopic variceal ablative procedure in the past were excluded from the study.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS; version 11.5, Chicago Inc.). The baseline characteristics were compared in the two groups (large and small varices) and results were expressed as either mean $\pm$ standard deviation, or median with interquartile ranges for all continuous variables depending on their distribution, and proportions/percentage for categorical data.

Univariate analysis was performed by using independent Student's *t* tests for continuous variables to compare the two groups. Categorical variables were evaluated using chi-square or Fisher exact test wherever appropriate. A *p* value <0.05 was considered statistically significant. All *p* values were two-sided. Variables with a *p* value of <0.25

on univariate analysis were included in stepwise multivariable logistic regression analysis to identify independent risk factors for LV.

Results

A total of 420 patients (264 men) presented with GEVH during the study period. The etiology of cirrhosis was hepatitis C virus (HCV) in 392 patients, hepatitis B virus (HBV) in 17, HBV and hepatitis D virus (HDV) coinfection in 5, infection with HBV, HCV, and HDV in 3, and unknown in 3 patients.

The mean time interval between admission and endoscopy was 14 h (range 4–28 h). A similar proportion of patients were on regular beta blocker therapy in the LV group (75/102, 73%) and SV group (216/318, 68%). Tables 1 and 2 show the clinical and laboratory/radiological parameters in the patients with SV and LV. Large varices were present in 24% of patients. The mean age, gender distribution, and presence of cirrhosis were similar in the two groups. The mean hemoglobin and s-albumin levels were lower, and the prothrombin time, and s-bilirubin levels were higher in the LV group, indicating more advanced disease; however, these did not assume statistical significance.

Liver cirrhosis with multicentric HCC, Child-Pugh class C, presence of clinically detectable ascites, grade 3–4 PSE, detectable splenomegaly, previous history of GEVH, and hemodynamic instability were more common in the LV group (Table 1). The frequency of unifocal HCC (9% vs. 7%) and PVT, both partial (10% vs. 11%) and complete (3% vs. 5%), in the LV and SV groups, respectively, were both similar.

The patients in the LV group had lower platelet counts in comparison to those in the SV group (91,000 vs. 113,000; $p = 0.028$) and larger splenic dimensions (158 mm vs. 115 mm; $p = 0.032$). The frequency of radiologically detected ascites, splenomegaly, and portal vein diameter were similar in both groups (Table 2).

On multiple logistic regression analysis, the independent predictors for the presence of LV were platelet count $<91,000$, cirrhosis with HCC, clinically detectable splenomegaly, splenic size ≥ 158 cm, hemodynamic instability, and a previous history of GEVH (Table 3).

Discussion

Severe upper gastrointestinal bleeding as a complication of portal hypertension develops in about 30–40% of patients with cirrhosis. Despite significant improvements in the

Table 1 Clinical variables at time of admission in patients with large and small varices

Parameter	Large varices ($n = 102$) 24%	Small varices ($n = 318$) 76%	p value
Age (years)	53 (36–72)	47 (32–62)	0.098
Gender (M/F)	67/35 (66/34%)	197/121 (62/38%)	0.092
Diagnosis			
Cirrhosis alone	71 (70%)	257 (81%)	0.089
Cirrhosis + MF HCC	24 (23%)	39 (12%)	0.040
Cirrhosis + PVT (complete)	3 (3%)	16 (5%)	0.099
Cirrhosis + HCC + PVT	4 (4%)	6 (2%)	0.088
Child-pugh class			
A	0 (0%)	24 (8%)	0.059
B	14 (14%)	84 (26%)	0.062
C	88 (86%)	210 (66%)	0.049
Ascites	$n = 99/102$ (97%)	$n = 210/318$ (66%)	
Clinically detected	72/99 (71%)	107/210 (51%)	0.045
PSE			
Absent	69 (68%)	251 (79%)	0.072
Stage 1 or 2	20 (20%)	45 (14%)	0.087
Stage 3 or 4	11 (12%)	22 (7%)	0.064
Splenomegaly	$n = 100/102$ (98%)	$n = 219/318$ (69%)	
Clinically detected	74/100 (74%)	88/219 (40%)	0.036
Previous history of GEVH	76 (74%)	95 (30%)	0.029
Hemodynamic instability	84 (82%)	172 (54%)	0.037

Abbreviations: MF HCC, multifocal hepatocellular carcinoma; PVT, portal vein thrombosis; GEVH, gastroesophageal variceal hemorrhage

Table 2 Laboratory/radiological parameters (mean/range) in patients with large and small varices

Parameter	Large varices (<i>n</i> = 102)	Small varices (<i>n</i> = 318)	<i>p</i> value
Hemoglobin (g/dL)	8.1 (5.1–10.8)	9.8 (6.9–11.8)	0.071
Platelets	91,000 (28–110,000)	113,000 (56–145,000)	0.028
Prothrombin time (s) ^a	21 (16.5–29)	17.5 (15.5–23)	0.065
s-bilirubin (mg/dL)	2.1 (1.4–17.6)	1.6 (0.9–12.4)	0.062
s-albumin (g/dL)	2.7 (1.6–2.8)	2.5 (2.1–3.4)	0.082
Ascites (Radiologically detected)	99/102 (97%)	178/210 (85%)	0.089
Splenomegaly (Radiologically detected)	100/102 (98%)	190/219 (87%)	0.078
Splenic size (mm)	158 (90–210)	115 (90–180)	0.032
Portal vein diameter (mm).	13.5 (10.5–13.9)	11 (10–12.3)	0.078

^a Control value 12 s**Table 3** Independent predictors of LV on multivariable logistic regression analysis

Parameter	Adjusted OR	95% CI	<i>p</i> value
Cirrhosis with HCC	8.5	2.1–32.9	0.029
Clinical splenomegaly,	5.8	2.3–10.8	<0.001
Hemodynamic instability	3.9	1.2–11.5	0.031
Previous history of GEVH	5.3	2.6–13.6	<0.001
Platelet count <91,000	30.6	11.2–13.8	<0.001
Splenic size ≥ 158 cm	4.1	2.4–12.9	0.006

early management of variceal hemorrhage, the mortality rate remains high [7].

While many studies have documented good predictive value of nonendoscopic variables for the presence or absence of varices, there is limited data regarding variables that could reliably and nonendoscopically predict the presence of large varices in decompensated patients. In our study, we considered only simple, commonly available, reproducible parameters, as we believe that other features that had previously been identified as noninvasive predictors of EV were less reproducible in clinical practice [27], were subject to interobserver variability [28], or were assessed in different ways even within the same study. Our study has demonstrated that platelet count <91,000, palpable splenomegaly, splenic size of 158 mm, hemodynamic instability, cirrhosis with hepatocellular carcinoma, and a previous history of GEVH are indicators of LV. A platelet cutoff of 91,000/mm [3] and a splenic diameter of 158 mm were chosen because they represented the median values and offered the best discrimination.

The importance of platelet counts has been alluded to in many studies [9–15]. In our study, the average platelet count of patients with LV was 91,000, compared to 113,000 for patients with SV. This is in line with existing studies that have documented LV with platelet counts below 100,000 [5, 9, 29]. While thrombocytopenia is an

important predictor of the presence of varices, a platelet count of below 100,000 nearly always predicts the presence of LV [5, 9, 22, 29].

Palpable splenomegaly and splenic size of 158 mm were important predictors of LV in our study. These reflect the severity of the underlying PHT, and patients with large varices would be expected to have these findings more often compared to patients with SV. Various authors have reported similar findings of an enlarged spleen being associated with the presence of varices [9–15, 29], but the presence of a clinically palpable spleen or radiological evidence of a spleen diameter >158 mm may serve as early clues to alert the physician to the presence of LV hemorrhage.

Hemodynamic instability was seen more frequently with bleeding from LV than with SV. The reason for this may be the higher portal pressure in patients with LV, which would result in more severe hemorrhage. The inherent cardiovascular abnormalities seen in cirrhosis, such as hypotension due to peripheral vasodilatation, and splanchnic vasoconstriction, and the vasoactive medications (e.g., diuretics, beta blockers), these patients may be taking may render these signs inconsistent [10, 12, 15]. Nevertheless, when present, these may be vital clues on clinical examination, pointing to the presence of LV and need for more aggressive resuscitation.

Hepatocellular carcinoma is an important precipitant of variceal hemorrhage [3]. While there are convincing data to show that patients with cirrhosis and HCC are more likely to suffer from variceal hemorrhage, limited data are available to predict the size of the varices found in these patients [30]. Our study has shown that this bleeding is more likely to be from LV than SV in this group of patients. While the percentage of patients with cirrhosis + HCC + PVT was more in the LV group, the number of patients was too small for a statistical difference to be observed.

A previous history of GEVH was also found to be an important indicator of LV in our study, as well as in the

literature [1, 7, 31, 32]. This most likely represents a continuum of events leading to progressively increasing PHT over a period of time, but may alert the physician early on that such a patient is likely to be bleeding from LV.

While studies like ours and other authors point to the importance of these variables in patients with EV, there are data to the contrary [33]. This underlines the need for studying these factors in a prospective, controlled setting.

In conclusion, cirrhosis with HCC, clinical splenomegaly, hemodynamic instability, a previous history of GEVH, thrombocytopenia (platelet count <91,000), and splenic size ≥ 158 mm are independent noninvasive predictors of large varices in patients hospitalized with gastroesophageal variceal hemorrhage.

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