Predictors of variceal bleed among patients with liver cirrhosis in the era of sclerotherapy

Varghese J, Cherian J V, Solomon R, Jayanthi V

ABSTRACT

Introduction: Variceal bleed is a common complication of portal hypertension. The bleed pattern has changed considerably with the introduction of variceal band ligation. The bleed pattern in developing countries where sclerotherapy continues to remain a viable option is not known. The aim of the study was to determine the predictors of first and subsequent bleed in individuals with liver cirrhosis.

Methods: 205 subjects with liver cirrhosis and portal hypertension registered in the liver clinic between January and June 2004, were followed-up for 18 months after registration. Bleeders already on pharmacotherapy or endotherapy were excluded. Patient details included age, gender, duration of illness, aetiology, Child-Pugh-Turcotte score and grades of oesophageal varices, details of index and subsequent variceal bleed, and complications during follow-up. Logistic regression multivariate analysis was applied to predict the factors influencing variceal bleed.

Results: There were 95 variceal bleeders and 110 non-bleeders. Age at presentation and gender did not predict a variceal bleed. Grades III and IV oesophageal varices and fundal varices were the significant risk factors for an index bleed (p-value is 0.001). 27 of the 95 bleeders (28.3 percent) had a second bleed after a mean interval of 8 (+/- 7.7) months. Predictors of rebleed were similar to the index bleed. Predictors of index bleed were also similar to those who had bled for the first time after registration. Overall bleed-related mortality was low (2.1 percent).

Conclusion: Higher grades of varices, presence of cherry-red spots and fundal varices predicted variceal bleed in patients with liver cirrhosis. Variceal bleed-related mortality was low in the era of sclerotherapy.

Keywords: endoscopic sclerotherapy, liver cirrhosis, oesophageal varices, variceal bleeding

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Department of Medical Gastroenterology, Stanley Medical College Hospital, Old Jail Road, Royapuram, Chennai 600001, Tamil Nadu, India

Varghese J, MD
Resident

Cherian J V, MD
Senior Resident

Solomon R, MD, DM
Assistant Professor

Jayanthi V, MD, DM
Professor and Head

Correspondence to:
Dr Joye Varghese
Tel: (91) 988 474 0103
Email: joyvargese@gmail.com

INTRODUCTION

Variceal bleed in patients with liver cirrhosis and portal hypertension manifests in 30%, with a one-year mortality of 50% after the initial bleed without treament.[1-6] The highest risk is within the first 48–72 hours, and more than 50% of all early rebleed episodes occur within the first ten days of cessation of an active bleed.[7-9] The scenario of variceal bleed in Indian subcontinent patients with liver cirrhosis is not known. A preliminary observation from our centre in 2003 had shown low rebleed rates after the index bleed.[10] This study had included variceal bleeders who were already on sequential sclerotherapy, thus resulting in a bias towards a low rebleed rate. A prospective study was therefore undertaken to determine the predictors of variceal bleed in liver cirrhosis patients in Chennai, Tamil Nadu, India, and followed-up for at least a year and half after registration. The data of variceal bleeders was compared to that of non-bleeders. A comparative analysis between index bleeders and those who had bled during the follow-up period was also made.

METHODS

Patients with liver cirrhosis belonging to any Child-Pugh-Turcotte (CPT) score category with oesophageal varices (excluding encephalopathy), presenting with or without a variceal bleed at registration or during the study period, i.e. between January and June 2004, were included in the study. Individuals with other sources of bleeding, such as erosions and duodenal ulcer at the time of emergency endoscopy, were excluded from the analysis. The diagnosis of cirrhosis was based on ultrasonographical criteria[11] and a CPT score exceeding six (CPT 5–6 points is classified as class A, 7–9 points as class B, and 10–15 points as class C). Liver biopsy was not considered for the inclusion criteria. The undertaking of the study was approved by the ethics committee of the institution.

Due to economic constraints, the management protocol for variceal injection sclerotherapy was 1.5% sodium tetradecyl sulphate at triweekly intervals until obliteration of varices, in combination with propranolol, on a dose titrated to reduce the pulse rate by 25% of the initial rate. For prevention, patients with grades III and IV oesophageal varices were managed with propranolol

Table I. Risk factors in variceal bleeders.

Variable	Variceal bleeders Group I (n = 95) No (%)	Non-bleeders Group II (n = 110) No (%)	p-value
Gender			
Male	63 (66.3)	89 (80.9)	0.17
Female	32 (33.7)	21 (19.1)	
Aetiology			
Unknown	41 (43.2)	28 (25.5)	0.006
Viral	23 (24.2)	49 (44.5)	
Ethanol	26 (27.4)	27 (24.5)	
Wilson's	5 (5.3)	6 (5.5)	
Grade of varices			
I & II	37 (38.9)	94 (85.5)	0.001
III & IV	58 (61.1)	16 (14.5)	
Cherry-red spot			
Present	5 (5.3)	1 (0.9)	0.03
Absent	90 (94.7)	109 (99.1)	
Fundal varices			
Present	18 (18.9)	5 (4.5)	0.001
Absent	77 (81.1)	105 (95.5)	
Diabetes mellitus			
Present	9 (9.5)	17 (15.5)	0.28
Absent	86 (90.5)	93 (84.5)	
Systemic hypertension			
Present	6 (6.3)	5 (4.5)	0.5
Absent	89 (93.7)	105 (95.5)	
CPT score			
A	70 (73.7)	32 (29.1)	0.04
B	25 (26.3)	73 (66.4)	
C	0 (0)	5 (4.5)	

prophylaxis on a dose that reduced the basal pulse rate by 25%.[12] None had a primary endoscopy prophylaxis. 12 patients who had endoscopy variceal band ligation during the study period were excluded from the study. Data entry included age, gender, duration of illness, aetiology and comorbid illness (diabetes mellitus, hypertension, hypothyroid state, renal disease). Dates of the first and subsequent variceal bleed, grades of oesophageal varices and/or fundal varices, and presence or absence of red signs at endoscopy were recorded.

Follow-up protocol during the 18-month period included recording of details of variceal bleed and cirrhosis-related complications. All the documented data between variceal bleeders and non-bleeders were compared. Baseline and six-monthly investigations included liver and renal function tests, ultrasonography and serum alpha-foetoprotein. Demographical and clinical data were expressed as frequency and percentage. Bivariate analysis of Pearson's chi-square test, Yates' corrected chi-square test and Fisher's exact test were used for calculating differences in the demographical and clinical data between the variceal bleeders and the non-bleeders. Logistic regression multivariate analysis was used to identify the significant risk factors.

RESULTS

205 of the 223 patients who registered between January and June 30, 2004 fulfilled the criteria and completed the study. 18 patients were lost to follow-up and could not be contacted. There were 145 male and 60 female patients. The mean age for men was 44 ± 15.1 years, and for women, 43 ± 14.3 years. There were 95 cirrhotic patients who had a variceal bleed during the study period, and 110 were non-bleeders. The male-to-female ratio in the two groups was 2:1 and 2.9:1, respectively. The duration of illness, the aetiology, the comorbid disease states and predictors of variceal bleed in the two groups are summarised in Table I. An average of six sessions of sclerotherapy (range varied from four to nine) downgraded the varices to grade I. One patient with fundal variceal bleed and failed sclerotherapy required emergency devascularisation.

On univariate analysis, age of presentation, gender, established aetiological factors and comorbid illness did not influence the risk of a variceal bleed. Unknown aetiology ($p = 0.006$), higher grades of varices (III and IV) ($p = 0.001$), presence of cherry red spots ($p = 0.03$), fundal varices ($p = 0.001$) and CPT class A score ($p = 0.04$) had significant influence over the bleed rates. Multivariate analysis (Table II) showed that patients with lower grade

Table II. Multivariate analysis using logistic regression.

Variable	Significance	Odds-ratio (95% CI)
Grade of varices	0.0001	4.35 (2.33–8.13)
Cherry-red spot	0.223	0.24 (0.03–0.3)
Fundal varices	0.042	3.14 (1.05–9.44)
Unknown aetiology	0.689	1.04 (0.8–1.22)

of varices (I and II) had four times lower risk of bleed and the presence of fundal varices placed the patients at a three-fold increased risk. However, unknown aetiology, cherry-red spot and CPT score did not affect the rebleed rates. 70 variceal bleeders presented with an index bleed and all belonged to class A. 38 (54.3%) of them progressed to class B. Subsequent variceal bleed occurred in 27 patients. The mean interval between the first and second variceal bleed in this subgroup was 8 ± 7.7 months. 14 patients bled for a third time after a mean interval of 7 ± 12.5 months. 13 (48.1%) patients had no further variceal bleed.

The risk factors that influenced the subsequent bleeds were similar to that of the initial bleed, except that the CPT score had now progressed to class B. Two deaths occurred due to a variceal bleed—one following surgery and the other due to failed medical and endotherapy; one each succumbed to hepatic encephalopathy, hepatorenal syndrome and hepatoma; and three developed spontaneous bacterial peritonitis. 25 (12.2%) patients who had not bled at the time of registration, bled for the first time after a mean period of 7 ± 8.6 months (range 1–15 months) during the 18-month follow-up. Two had a second bleed at a mean interval of five months. Comparing index bleeders and bleeders on follow-up, except for CPT score, there was no significant difference (Table III). Four succumbed to hepatic encephalopathy and two to hepatorenal syndrome. None developed spontaneous bacterial peritonitis or hepatocellular carcinoma.

DISCUSSION

The present study prospectively looked into the bleed pattern among cirrhotic patients with portal hypertension in a South Indian population. The statistically significant variables which differentiated a variceal bleeder from a non-bleeder during the 18-month follow-up were large-sized varices, cherry-red spots and fundal varices, both for the index bleeders and subsequent bleeders. The results are similar to those reported by other studies.[13,14] Kleber et al, however, found that CPT score did not influence the bleed rates, but did influence the mortality.[15] A high risk of index bleed has been attributed to continued alcohol

Table III. Comparison of index bleeders and bleeders on follow-up.

Variable	Index bleeders (n = 70) No (%)	First bleed during follow-up (n = 25) No (%)	p-value
Gender			
Male	45 (64.3)	17 (68)	0.61
Female	25 (35.7)	8 (32)	
Aetiology			
Unknown	30 (42.9)	9 (36.0)	0.76
Viral	16 (22.9)	7 (28.0)	
Ethanol	18 (25.7)	8 (32.0)	
Wilson's	6 (8.6)	1 (4.0)	
Grade of varices			
I & II	19 (27.1)	10 (40.0)	0.15
III & IV	51 (72.9)	15 (60.0)	
Cherry-red spot			
Present	6 (8.6)	1 (4.0)	0.65
Absent	64 (91.4)	24 (96.0)	
Fundal varices			
Present	18 (25.7)	3 (12.0)	0.06
Absent	52 (74.3)	22 (88.0)	
Diabetes mellitus			
Present	8 (11.4)	2 (8.0)	0.44
Absent	62 (88.6)	23 (92.0)	
Systemic hypertension			
Present	9 (12.9)	1 (4.0)	0.11
Absent	61 (87.1)	24 (96.0)	
CPT score			
A	19 (27.1)	2 (8.0)	0.02
B	49 (70.0)	21 (84.0)	
C	2 (2.9)	2 (8.0)	

Value are rounded to one decimal place

use,[15] poor liver function (CPT class C) and ascites.[1] Alcohol and viruses did not increase the risk of index bleed in the present series, unlike the reports by others.[16] A high incidence (30%–50%) of rebleed rate has been documented after endoscopic sclerotherapy.[17-19] Attributable factors include age > 60 years, haemoglobin level < 8 g/dL, large varices, clot on varices, actively bleeding varices, renal failure and ascites.[9,10,16,20] The rebleed rate at 18 months in the present series was 29.4%, figures similar to the North Italian Endoscopic Club (NIEC) multicentric report of 26.5% over a median period of 23 months,[1] and other studies.[13,14] The risk factors for variceal rebleed in the present series were similar to that of the initial bleed, and not much of a difference was noted in the interval between the first and second, and between second and third, bleed; results comparable to the NIEC report.

Survival rates after index bleed without treatment have varied from 32% to 80%.[7,21,22] Each subsequent bleed is associated with at least a 20%–30% risk of death.[9,20] Repeated injection sclerotherapy eradicated oesophageal varices in most long-term patients, and complete eradication of varices reduced rebleeding and death from oesophageal varices.[23,24] The probability of treatment failure is significantly higher in CPT class C patients with gastric varices.[19] Despite control of variceal bleeding, survival at five years was only 26%, because of death due to liver failure in most patients.[25] Mortality rate in our series due to variceal rebleed following endoscopic sclerotherapy was 2% at 18 months follow-up. In summary, the risk of variceal bleed among cirrhotics in our series is directly related to the grades of varices, results similar to that reported in the West. Variceal rebleed rates and bleed-related mortality are low in the era of sclerotherapy.

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