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PREDICTIVE FACTORS OF BLEEDING FROM ESOPHAGEAL VARICES IN PATIENTS WITH LIVER CIRRHOSIS AND PORTAL HYPERTENSION

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Summary. *Variceal bleeding is the most life-threating complication in liver cirrhosis. The aim of this study was to ascertain the risk factors of bleeding from esophageal varices.52 patients with liver cirrhosis and portal hypertension were included in prospective study. We analyzed the severity of liver dysfunction according to Child's classification, coagulation parameters, and endoscopic parameters: size, color, location of varices, and the presence of "red signs". Varices were classified as small, medium and large.Esophageal varices were found in 76.9% of the patients with liver cirrhosis and portal hypertension. Small varices were present in 10%, medium in 25% and large in 65% patients. 55% of them had variceal bleeding. Variceal bleeding was present in 50% patients with medium and in 65.38% patients with large varices. There was no bleeding in patients with small varices.Endoscopy revealed "red signs" before bleeding in 85% patients with large varices. There was a higher incidence of variceal bleeding in Child's group B. There were no significant differences ($p>0.05$) of the coagulation parameters in patients with and without variceal bleeding. Rebleeding was present in 86.36% patients. Most of them (52.63%) rebled between 7 weeks and 12 months after the first episode of variceal bleeding. In the patients with the most severe hepatocellular dysfunction (Child's group C) period between the first bleeding and rebleeding was the shortest (mean 20.8 days). Our study revealed association between the first bleeding and large varices and the "red signs". Coagulation disorders and hepatic dysfunction were not related to the initial episode of variceal bleeding. The risk of early rebleeding was higher in patients with severe hepatic dysfunction (Child's class C).*

Key words: *Risk factors, variceal bleeding, esophageal varices, portal hypertension, cirrhosis hepatis*

Introduction

Variceal bleeding is the most serious complication of portal hypertension (1-7). Gastroesophageal varices are present in 50–60% of cirrhotic patients and about 30% of these patients will experience an episode of variceal hemorrhage within one year of the diagnosis of varices (4-8). After the initial bleed, the risk of variceal rebleeding reported in the literature ranges from 50-80%. About one half of all rebleeds occur within the first six weeks (7). Risk of rebleeding is very high in survivors of an episode of hemorrhage; in approximately 70% of patients, this will occur in the first few days following the first hemorrhage.

The aim of our prospective study was to evaluate the value of some endoscopic, clinical and laboratory parameters in the prediction of initial variceal bleeding and rebleeding in patients with liver cirrhosis.

Materials and Methods

Fifty two patients with liver cirrhosis and portal hypertension were included in prospective study from January 2003 through January 2006. Thirty for were male and 18 female. The mean age was 56.6 years (range, 39 to 86). At entry, a full medical history was taken. All patients underwent a complete physical and routine laboratory examination. As predictive factors for variceal bleeding we analyzed the severity of liver dysfunction, coagulation parameters, and endoscopic parameters – size and localization of varices, and presence of "red signs".

The severity of liver disease was assessed according to Child's classification (Table 1) (3).

Table 1. Child's classification of hepatocellular dysfunction in liver cirrhosis. Adapted from Sherlock and Dooley (9)

Child's Group	A	B	C
Serum Bilirubin (mg/dl)	<2.0	2.0-3.0	>3.0
Serum Albumin (g/dl)	>3.5	3.0-3.5	<3.0
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced coma
Nutrition	Excellent	Good	Poor ("wasting")

The standard coagulation parameters - platelet count, prothrombin time (PT), partial thromboplastin time

(PTT), thrombin time (TT), F II, F V and F VII were determined for each patient.

All patients underwent upper endoscopy. The diagnosis of variceal bleeding was confirmed if an actively bleeding varix or a varix with adherent clot was seen. At entry, the following endoscopic features were recorded: size, color, and location of varices, and the presence of "red signs".

The size of varices was classified according the following criteria:

1. Small (F1): the varices can be depressed by the endoscope.
2. Medium (F2): the varices cannot be depressed by the endoscope.
3. Large (F3): the varices are confluent around the circumference of the esophagus.

Results

Esophageal varices were found in 40 (76.9%) of the patients with liver cirrhosis and portal hypertension. Small varices were present in 4 (10%) patients, medium varices in 10 (25%) patients and large varices in 26 (65%) patients. Twenty two (55%) of them had variceal bleeding. Variceal bleeding was present in 5 (50%) patients with medium and in 17 (65.38%) patients with large varices. There was no bleeding in patients with small varices.

Endoscopy revealed "red signs" before bleeding in 85% patients with large varices. Associated esophageal and gastric varices were found in two patients with variceal bleeding.

According to Child's classification of hepatocellular dysfunction in liver cirrhosis, the patients were classified into 3 groups. There was a higher incidence of variceal bleeding in group B (11 of 19 patients, 57.89%) and group A (6 of 10 patients, 60%) in comparison with group C (5 of 11 patents, 45.45%) (Fig. 1).

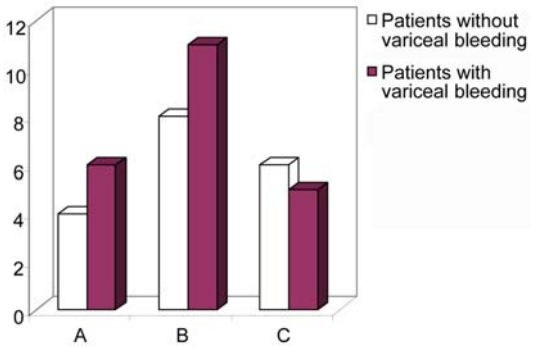

Fig. 1. Child's class in relation to variceal bleeding

The value of coagulation parameters in patients with variceal bleeding and patients without variceal bleeding are shown in Table 2. There were no significant statistical differences ($p > 0.05$) in the platelet count, prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), F II, F V, and F VII between the patients with and without variceal bleeding.

Table 2. Coagulation parameters in patients with and without variceal bleeding

Coagulation parameter	Patients with variceal bleeding X1 ± SD1	Patients without variceal bleeding X2 ± SD2	χ^2 test t	p
Platelet count	89.71±50.78	106.88±55.82	1.01	> 0.05
Prothrombin time (PT)	16.83± 2.45	17.25± 3.99	0.86	> 0.05
PTT	56.71±14.64	59.06±12.85	0.52	> 0.05
Thrombin time (TT)	18.58± 1.26	20.75± 8.16	1.29	> 0.05
F II	56.75±16.44	50.63±11.69	1.29	> 0.05
F V	58.00±22.26	63.31±21.94	0.74	> 0.05
F VII	46.08±19.05	42.69±23.54	0.50	> 0.05

Mean following time after initial bleeding was 17 months. Rebleeding was present in 19 (86.36%) patients. Most of them, 10 (52.63%) rebled between 7 weeks and 12 months after the first episode of variceal bleeding. Seven (36.84%) patients had rebleeding in the first six weeks and 2 (10.53%) patients in the second year after the first episode of variceal bleeding (Table 3).

Table 3. Time of rebleeding after the first variceal bleeding

Time of rebleeding after the first variceal bleeding	Number of patients n	%
Six week	7	36.84
Seven weeks to 12 months	10	52.63
In the second year	2	10.53

In the patients with the most severe hepatocellular dysfunction (Child's group C) the period between the first bleeding and rebleeding was the shortest (mean 20.8 days). The patients from Child's group A had a longer period free of variceal bleeding (mean 226.7 days) (Table 4).

Table 4. The mean period between the first variceal bleeding and rebleeding

Child's class of hepatocellular dysfunction	Mean period without bleeding (days)
A	226.7
B	106.7
C	20.8

Discussion

Variceal hemorrhage is a major source of mortality of patients with portal hypertension (1-7). According to the literature, gastroesophageal varices are present in 50-60% of cirrhotic patients) The natural history of liver cirrhosis shows that 30% of patients with liver cirrhosis will experience an episode of variceal hemorrhage within one year of diagnosis of varices (4-8). The incidence of gastroefophageal varices in our study is higher.

We found gastroesophageal varices in 76.9% of patients with liver cirrhosis and portal hypertension, and 55% of them had variceal bleeding.

Our study has shown that large varices are more likely to bleed than small ones. Bleeding was present in 65.8% of our patients with large varices and in 50% with medium varices. Small varices did not bleed. Wall tension is a factor of diameter and wall thickness, and it is not supprising that larger varices are more likely to rupture. Variceal size has been investigated by many researchers (10-15). All of them have documented the fact that larger varices bleed more often than smaller varices (Table 5). The only exception to this is a study done by Kock *et al*. (13), who found that 35% of patients with small varices bled, while only 20% of patients with large varices also bled.

Table 5. Size of gastroesophageal varices and variceal bleeding in cirrhotic patients without previous bleeding

	Variceal size					
	Small		Medium		Large	
Author	n	%	n	%	n	%
Peglioro *et al.* (12)	–	6	–	–	–	25
Burroughs *et al.* (15)	–	10	–	–	–	35
Witzel *et al.* (14)	20	35	15	53	18	83
Kock *et al.* (13)	20	35	–	–	10	20
NIEC (11)	160	18	112	29	49	49
Benedeto-Stojanov *et al.*	–	-	5	50	17	65.38

In the study o the Nortern Italian Endoscopic Club (NIEC), six endoscopic parameters were significantly related to variceal bleeding (11). Two of these parameters were variceal size and location. Larger and more superior varices had a higher bleeding rate. We found associated esophageal and gastric varices in two patients who bled.

Another endoscopic finding of value in predicting variceal bleeding is the appearance of the vessel wall. The color of varices is thought to predict impending hemorrhage. Our study has shown that endoscopic finding of "red signs" is related to the variceal bleeding. The "red signs" were found in 85% of large varices with bleeding. The red color signs are the result of microteleangioectasia of the varix. Variants of this sign are red wale marks, which look like whip marks; chery red spots 2mm in diameter; hemocystic spots, which are round, crimson projections larger than 4mm that look like blood blisters; and diffuse redness. "Cherry red spots" were noted to be dilated subepithelial veins. Hematocystic spots represent blood exiting from the deeper esophageal veins into the superficial submucosal veins. The "fundamental" color of the varices is blue or white. All the red color signs and a blue color of one varix are thought to be risk factors for bleeding.

The study of NIEC showed that there was a strong correlation between a patient's Child class at the time of endoscopy and the rate of bleeding during the followup (11). Most of our patients with variceal bleeding were Child's class B followed by patients with Child's class A. Ascites, hyperbilirubinemia, hypoalbuminemia, and high prothrombin time were also factors that significantly increased the risk of variceal bleeding in NIEC study. Our study has shown no significant differences in the value of cogulation parameters in patients who bled and those who did not.

The analysis of relation between the clinical and endoscopic parameters in the NIEC study has shown three variables to have independent prognostic significance for variceal bleeding: Child's class, size of varices, and the presence of red wale markings. These three variables were largely independent of each other, although size of varices and presence of red wale markings appeared somewhat related. In our study the "red signs" were found in 85% of large varices with bleeding. A prognostic index for variceal hemorrhage using the three variables of variceal size, red wale marks, and a modified Child classification of the underlying liver disease, is able to identify subset of patients with a 1-year incidence of bleeding ranging from 6% to 76%. The value of these predictors for variceal rupture depends on the usefulness of prophylactic therapy for variceal bleeding.

The risk of variceal rebleeding after the initial bleed reported in the literature ranges from 50% to 80% (1, 7). Our study has shown higher rate of rebleeding. After the initial bleed, rebleeding was present in 86.36% of our patients in a mean following period of 17 months. As it has been reported in the literature, approximately one-half of all rebleeds occur within the first six weeks. Beyond the sixth week after the initial bleeding episode, the risk of further bleeding returns to the same level of risk as in patients who have never bled (i.e., 30% within one year) (4-8). Data from our study are different. Most of our patients (52.35%) had rebleeding in a period between 7 weeks and 12month after the initial bleeding. In the first 6 weeks after the initial bleeding, rebleeding was present in 36.84% patients, and beyond one year in 10.53% patients.

The most effective indicators of risk of early rebleeding are reported to be the parameters that reflect the degree of hepatic dysfunction. These include the presence of ascites, hypoalbuminemia, low prothrombin activity, encephalopathy and hyperbilirubinemia (9, 15-17). Our study has shown that patients with the most severe hepatocellular dysfunction (Child's group C) have the shortest period between the first bleeding and rebleeding (mean 20.8 days). The patients from Child's group A had a longer period free of variceal bleeding (mean 226.7 days) (Tab.4.).

In conclusion, our study revealed association between the first bleeding and large varices and the "red signs". Coagulation disorders and hepatic dysfunction were not related to the initial episode of variceal bleeding. The risk of early rebleeding was higher in patients with severe hepatic dysfunction (Child's class C).

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PREDIKTIVNI FAKTORI KRVARENJA IZ EZOFAGEALNIH VARICESA U BOLESNIKA SA CIROZOM JETRE I PORTNOM HIPERTENZIJOM

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Kratak sadržaj: *Krvarenje iz varikoziteta je najteža komplikacija ciroze jetre. Cilj naše studije je procena faktora rizika za krvarenje iz ezofagogastričnih varikoziteta. Prospektivnom studijom obuhvaćeno je 52 bolesnika sa cirozom jetre i portnom hipertenzijom. Analizirna je težina insuficijencije jetre po Child klasifikaciji, koagulacioni parameteri i endoskopski parameti: veličina, boja i lokalizacija varikoziteta i prisustvo "red signs". Po veličini varikoziteti su klasifikovani kao mali, srednji i veliki. Ezofagealni varikoziteti su dijagnostikovani u 76.9% bolesnika sa cirozom jetre i portnom hipertenzijom. Mali variksi su bili prisutni u 10%, srednji u 25% i veliki u 65% bolesnika. Varikozno krvarenje je nadjeno u 55% bolesnika. Varikozno krvarenje je bilo prisutno u 50% bolesnika sa srednjim i u 65.38% bolesnika sa velikim variksima. Bolesnici sa malim variksima nisu krvarili. U 85% bolesnika sa velikim varikozitetima endoskopija je pokazala "red signs". Nadjena je veća incidenca varikoznog krvarenja u B grupi po Child-u. Nije bilo signifikantne razlike ($p>0,05$) koagulacionih parametara u bolesnika sa i bez varikoznog kvarenja. Rekrvarenje se javilo u 86,36% bolesnika. Većina (52,63%) je imalo rekrvarenje izmedju sedme nedelje i 12 meseci posle inicijalnog krvarenja. Period izmedju prvog krvarenja i rekrvarenja je bio najkraći (20,8 dana) u bolesnika sa najtežim stepenom insuficijencije jetre (Child C). Naša studija je pokazala da je varikozno krvarenje u vezi sa velikim variksima i prisustvom "red signs". Koagulacioni poremećaji i hepatična disfunkcija nisu bili u vezi sa inicijalnom epizodom varicealnog krvarenja. Rizik ranog rekrvarenja je bio veći u pacijenata sa teškom insuficijencijom jetre (Child C).*

Ključne reči: *faktori rizika, varicealno krvarenje, ezofagealni varicesi, portna hipertenzija, ciroza jetre*