ORIGINAL CONTRIBUTION

Risk Factors for Variceal Bleeding

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Variceal bleeding is the most serious complication of portal hypertension. It is seen in 50-60% patients with cirrhosis. The mortality in patients who develop gastroesophageal variceal bleeding is approximately one third. In patients who have never bled from esophageal varices, 30% will hemorrhage within one year after the diagnosis of varices. The risk of bleeding after the initial bleed has been reported in the literature to be between 50 and 80%. In addition, 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). With these figures in mind, it is important to be aware of the risk factors for gastroesophageal variceal hemorrhage. This paper examines the risk factors that may help identify patients most likely to bleed or rebleed. Specifically, risk factors for : 1) initial bleeding 2) early rebleeding (bleeding within six weeks of the initial bleed) and 3) late rebleeding (greater than six weeks from the initial bleed) are discussed.

INTRODUCTION

The three major consequences for patients with portal hypertension are the development of a portosystemic collateral circulation, bleeding from gastroesophageal varices, and ascites. Provided that the patient does not succumb to progressive liver failure, the terminal event in many cases is catastrophic bleeding from gastroesophageal varices.

Variceal hemorrhage is the most dreaded complication of portal hypertension. It accounts for approximately one-third of the mortality in cirrhotic patients (1-3). 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 (2-7). Approximately 10-15% of cirrhotics without varices develop them *de novo* each year (3).

After the initial bleed, the risk of variceal rebleeding reported in the literature ranges from 50% to 80% (1). One useful way of stratifying patients into risk groups is by using the Child classification system (8). This system is based on several clinical parameters indicative of the severity of hepatic dysfunction (**Table 1**). Thus, 25% of class A, 50% of class B and 75% of class C patients with cirrhosis will have rebled within one year (8). About one-half of all rebleeds occur within the first six weeks (9). The risk of rebleeding decreases with time such that by the sixth week after the first episode of variceal bleeding, the risk of further bleeding returns to baseline values, approaching the risk of bleeding in patients who have never bled (1). After the first six weeks, recurrent bleeding accounts for about 25-40% of the mortality per episode of bleeding (5). Furthermore, several studies have assessed the severity of the liver disease according to the Child's classification and the corresponding mortality from variceal bleeding (**Table 2**).

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 index hemorrhage (10).

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RISK FACTORS FOR THE INITIAL BLEED

Clinical Parameters

Alcohol Abuse. It is well known that if alcoholic cirrhotics abstain from drinking, remarkable improvements in their clinical status will occur. In all studies involving cirrhotic patients who had not bled previously, abstaining from alcohol led to an improvement in the severity of the liver disease as well as a reduction in the risk of variceal bleeding (3). Studies have shown that the risk of rebleeding in these patients ranged from 0% to 15% (3). Conversely, persistent alcohol abuse was associated with a higher risk of bleeding, ranging from 32% to 47% in the same studies.

Table 1: *Child's classification of hepatocellular dysfunction in liver cirrhosis. Adapted from Sherlock and Dooley (8).*

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")

Table 2: *Estimated natural history of variceal bleeding in cirrhosis of the liver, according to the Child classification. Adapted from De Franchis and Primigani (3).*

Child's Group	1-Month Mortality (%)	1-Year Survival Rate (%)	2-Year Survival Rate (%)
A	<10	76	65
B	30	52	39
C	>45	35	23

Liver Decompensation. Many studies have shown that ascites is strongly associated with gastroesophageal bleeding (11-14). Conn *et al.* showed that persistent ascites was three times more common in patients who bled than in those who did not (12). Similarly, Resnick *et al.* documented that persistent ascites was present in 25% of patients who bled and only 10% in those who did not bleed (13). Furthermore, a study by the Northern Italian Endoscopic Club (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 follow-up (**Table 3**) (14). Ascites, hyperbilirubinemia, hypoalbuminemia, and high prothrombin time were also factors that significantly increased the risk of variceal bleeding. Burroughs *et al.* also showed that the rate of deterioration of liver function appeared to be faster in patients who bled when compared to those who did not (15) .

Table 3: *Child's class in relation to variceal bleeding. Adapted from the NIEC (14).*

Child's Class	# Patients	% who Bled	P value
A	135	17.0	<0.0001
B	132	31.1	
C	54	38.9	

Endoscopic Parameters

Variceal size has been investigated by many researchers (3,14-18). All of them have documented the fact that larger varices bleed more often than smaller varices (**Table 4**). The only exception to this is a study done by Koch *et al.* who found that 35% of patients with small varices bled while only 20% of patients with large varices also bled (8). The size of gastroesophageal varices was noted using 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.

In another study by the NIEC (14), six endoscopic parameters were significantly related to variceal bleeding. Two of these parameters were variceal size and location (whether they were superior, inferior or median). Larger and more superior varices had a higher bleeding rate. Other endoscopic parameters included the presence of red wale markings, "cherry red spots", diffuse redness, and hematocystic spots. "Cherry red spots" were noted to be dilated subepithelial veins. Hematocystic spots were documented as being approximately 4 mm in diameter and representative of blood exiting from the deeper esophageal veins into the superficial submucosal veins.

Table 4: *Size of gastroesophageal varices and variceal bleeding in cirrhotic patients without previous bleeds. Adapted from De Franchis and Primignani (3).*

	Variceal Size					
	Small		Medium		Large	
Author	Number	% Who Bled	Number	% Who Bled	Number	%Who Bled
Paglioro et al (16) (n=99)	-	6	-	-	-	25
Burroughs et al (9) (n=106)	-	10	-	-	-	35
Witzel et al (18) (n=53)	20	35	15	53	18	83
Kock et al (17) (n=30)	20	35	-	-	10	20
NIEC (14) (n=321)	160	18	112	29	49	49

Combination of Clinical and Endoscopic Parameters

The relation between the clinical and endoscopic parameters was also analysed in the NIEC study (14). Only three were shown 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. The prevalence of large varices was 17% in Child's class A, 14% in class B, and 13% in class C patients. Similarly, the prevalence of red wale markings was 33% in class A, 41% in class B and 39% in class C patients. In addition, red wale markings were found in 21% of patients with small varices, 42% of those with medium varices and 80% of those with large varices. Among patients with equal variceal size, those with red wale markings bled twice as often as those without.

Thus, the three variables were then used to calculate a prognostic index, known as the NIEC index. This index was used to calculate the risk of bleeding in cirrhotic patients (a) within six months and (b) within one year of the initial bleed. It was computed by adding the three variables (**Table 5**). Only one number was used for each variable. With the use of the NIEC index, patients were subdivided into risk classes according to the value of their NIEC index at entry (**Table 6**). The NIEC index has been validated in three independent studies of more than 600 patents in total (14,19-20). They all show the validity of the index in assessing the risk of bleeding in new patients. Because of other factors that are difficult to assess (and which may be important in causing the variceal rupture), such as varicele rupture, the NIEC Index cannot be considered ideal.

Hemodynamic Parameters

Several investigators have shown that there is a threshold value of portal pressure approximately 12 mm Hg when the pressure is measured as hepatic vein pressure gradient (HVPG). Portal pressures less than this did not present with variceal formation and thus variceal hemorrhage (1). However, this pressure threshold is a necessary but not sufficient condition for the varices to develop. Varices develop in only some of the patients with an HVPG greater than 12 mm Hg. In addition, no linear relationship exists between HVPG values and variceal size. In another study, patients in whom the HVPG dropped to below 12 mm Hg showed a significantly larger reduction in variceal size, a lower incidence of variceal hemorrhage, and a reduced mortality compared to the patients in whom the HVPG remained greater than 12 mm Hg (21). Nevertheless, in the same study, HVPG value was not shown to have a predictive effect on variceal bleeding.

Variceal pressure can be measured by two equally precise methods during endoscopy. One requires direct variceal puncture and the other involves the use of pressure gauges that measure variceal pressure without puncturing the variceal wall (3). There is no data which shows whether measurement of the variceal pressure can be used prospectively to identify patients at high risk of bleeding.

Table 5: *Calculation of the NIEC index. Adapted from the NIEC (14).*

Variable	Points To Add
Child's Class	
A	6.5
B	13.0
C	19.5
Size of Varices	
Small	8.7
Medium	13.0
Large	17.4
Red Wale Markings	
Absent	3.2
Mild	6.4
Moderate	9.6
Severe	12.8

RISK FACTORS FOR EARLY REBLEEDING (WITHIN 6 WEEKS AFTER THE INITIAL EPISODE)

Clinical Parameters

The parameters that reflect the degree of hepatic dysfunction are the most effective indicators of the risk of early rebleeding. These include the presence of ascites, hypoalbuminemia, low prothrombin activity, encephalopathy and hyperbilirubinemia (3,5). Other parameters have been shown to have a predictive effect including an age over 60, the severity of the initial bleed (expressed by the presence of severe anemia or hypotension) and the presence of impaired renal function (expressed by increased values of blood urea nitrogen or serum creatinine)(2,3,5,9). Finally, as mentioned previously, the time of the initial bleed is an important determinant of the risk of rebleeding as the risk decreases as a function of time (2,3,5,9).

Endoscopic Parameters

Many studies have shown a significant correlation between presence of active bleeding at the time of emergency endoscopy and the subsequent risk of rebleeding (3). In addition, the size of the varices has been shown to be a risk factor in that the presence of large varices can predict rebleeding, either early (within 6 weeks of the initial bleed) or late (after 6 weeks) (3,5).

RISK FACTORS FOR LATE REBLEEDING (GREATER THAN 6 WEEKS FROM THE INITIAL EPISODE)

Clinical Parameters

Much like the risk factors for early rebleeding, the risk factors for late rebleeding are related to the severity of the liver disease. Specifically, the presence of ascites, encephalopathy, and hypoalbuminemina are most important (3). Furthermore, it has been shown that in patients with alcoholic cirrhosis, the persistence of alcohol intake increases the risk significantly. Finally, the development of hepatocellular carcinoma has also been correlated with an increased risk of late rebleeding (3).

Endoscopic Parameters

The only endoscopic parameter proven to be a significant prognostic indicator for late rebleeding is variceal size (3). Not surprisingly, the larger the varices, the higher the rate of rebleeding.

CONCLUSION

There is no doubt that bleeding from gastroesophageal varices is a major source of mortality for patients with portal hypertension. Several risk factors have been discussed in this paper that may help identify patients at high risk. In patients who have never had a hemorrhage, clinical, endoscopic and hemodynamic factors were important. Clinical factors included continued alcohol abuse and the degree of liver decompensation, as measured by the Child classification system. The most important endoscopic parameters included size and location of gastroesophageal varices, presence of red wale markings, hematocystic spots, "cherry red spots", and diffuse

Table 6: *Cumulative proportion of patients bleeding among 321 cirrhotic patients with varices, classified according to the NIEC index at entry. Adapted from the NIEC (14).*

	Rate of Variceal Hemorrhage (%)	
NIEC Index At Entry	Six Months	One Year
</= 20.0	0.0	1.6
20.1 - 25.0	5.4	11.0
25.1 - 30.0	8.0	14.8
30.1 – 35.0	13.1	23.3
35.1 – 40.0	21.8	37.8
>40.0	58.5	68.9

redness. The NIEC index was used as a prognostic indicator because it was based on a combination of clinical and endoscopic parameters. Finally, hemodynamic risk factors for the initial hemorrhage included the HVPG, a measurement of portal pressure.

In patients who have had their initial episode of bleeding, risk factors for rebleeding within six weeks included various clinical and endoscopic parameters. The clinical parameters that were significant included the degree of hepatic decompensation, an age greater than 60 years, the severity of the initial hemorrhage, and the presence of impaired renal function. Endoscopic parameters that were important included the size of the varices and evidence of active bleeding.

The most important risk factors that were significant for rebleeding beyond six weeks of the initial bleed included the level of hepatic decompensation, the development of hepatocellular carcinoma, and the persistence of alcohol intake. The size of the gastroesophageal varices has been the only endoscopic parameter proven to be significant in predicting late rebleeding.

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