

The Value of Renal Artery Resistive Indices: Association with Esophageal Variceal Bleeding in Patients with Alcoholic Cirrhosis¹

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Purpose: To determine whether resistive indices of the renal artery (RIR) or the splenic artery (RIS) can be used as predictors of bleeding in patients with alcoholic liver cirrhosis.

Materials and Methods: According to esophageal variceal bleeding episodes, 33 patients with cirrhosis were divided into two groups, a bleeder group ($n = 17$) and a non-bleeder group ($n = 16$). These two groups were compared with respect to five variables (age, spleen size, Child's score, RIS, and RIR). Sensitivity, specificity, and accuracy for the detection of bleeders were calculated using a cutoff value of 0.7 for RIR.

Results: The mean values of variables were higher for bleeders than for non-bleeders. With the exception of age, four variables were significantly correlated with bleeding ($r = 0.43$ for spleen size; $r = 0.36$ for Child's score; $r = 0.37$ for RIS; $p < 0.05$, respectively; $r = 0.63$ for RIR, $p < 0.01$). Only RIR was found to be significantly a predictive variable for bleeders (adjusted Odds ratio = 19.9; 95% confidence interval: 1.3 - 306, $p < 0.05$) when the RIR was more than 0.7. RIR had a sensitivity of 88.3% and a specificity of 75% with an accuracy of 81.8% at a cutoff value of 0.7 for identifying bleeders.

Conclusion: A high RIR value will be useful in predicating esophageal variceal bleeding in patients with alcoholic liver cirrhosis.

Index words : Ultrasound (US), Doppler studies
Liver cirrhosis
Esophagus, varices

Bleeding from ruptured esophageal varices is the main complication of portal hypertension and is a major cause of death in patients with cirrhosis, and occurs more frequently in patients with alcoholic cirrhosis. The most important predictors related to the risk of bleeding are variceal size, the severity of liver dysfunction (as ex-

pressed by the Child-Pugh classification), and red wale marks (1). As the predictive power of this index is far from satisfactory, the current consensus is that all cirrhotic patients should be endoscopically screened for varices at the time of diagnosis (1). In order to reduce the increasing burden placed on endoscopy units, considerable efforts have been made to identify hemodynamic indicators of the risk for variceal bleeding, noninvasively, by Doppler ultrasound (2, 3). However, the sensitivity and specificity of this modality for detecting patients at risk for bleeding are low.

The key factor in the natural history of esophageal

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varices is increased portal pressure, which for cirrhosis is caused by a combination of increased hepatic vascular resistance and increased portal collateral blood flow. Therefore, increased portal pressure and the volume of blood flow are likely to be the most important factors associated with esophageal variceal bleeding (2).

In the present study, we evaluated two noninvasive Doppler parameters as indicators of portal pressure and hyperdynamic circulation: first, the resistive index of the splenic artery (RIS), which has been well correlated with transhepatic portal pressure (4) and second, the resistive index of the renal artery (RIR), which indicates a worsened hemodynamic status resulting in increased collateral blood flow. The aim of this study was to evaluate retrospectively RIS and RIR in terms of their abilities to predict bleeding in alcoholic cirrhosis patients. The identification of factors predictive of bleeding in these patients is of pivotal importance to identify those patients requiring prophylactic treatment.

Materials and Methods

Patients and Clinical Features

Patients were consecutively selected from a series of 33 individuals with alcoholic cirrhosis who received follow-up at our institution between June 2004 and July 2005. Approval or informed consent for access to patients records and images was obtained. Patients eligible for this retrospective study were those with clinically proved alcoholic cirrhosis who had primarily received conservative treatment or variceal ligation, and who had

undergone Doppler ultrasonography. The diagnosis of cirrhosis was determined by clinical history, laboratory data, and the use of CT or ultrasound imaging. Liver biopsy was not performed on the patients. The patients were divided into two groups, a bleeder group ($n=17$) and a non-bleeder group ($n=16$), according to the presence/absence of variceal bleeding episodes. A mean bleeding rate of patients was 2.2 episodes. The clinical status of the study subjects were Child's A in 21 cases, Child's B in 10 cases, and Child's C in 2 cases; all of the patients had a serum creatinine concentration of <1.5 mg/dL and no nephrologic abnormality at the time of the clinical study.

Doppler US Exams

All ultrasonographic examinations were performed using a Sequoia 512 scanner (Siemens Medical Solutions, Mountain View, CA U.S.A.) with a convex 3-5 MHz transducer. The interval between esophageal bleeding and Doppler sonography was 3 ± 1.3 days. For spleen evaluations, the transducer was positioned below the left costal margin or in the left costal space. To quantify splenic sizes, maximum longitudinal diameters were measured in coronal plane sections, with visualization of the splenic hilum. RIS values were measured intraparenchymally near the hilum (Figs. 1, 2). For kidney evaluations, Doppler signals were obtained from the interlobar arteries along the borders of the medullary pyramids (Figs. 1, 2). All RI measurements were performed in triplicate and means were taken as definitive values.

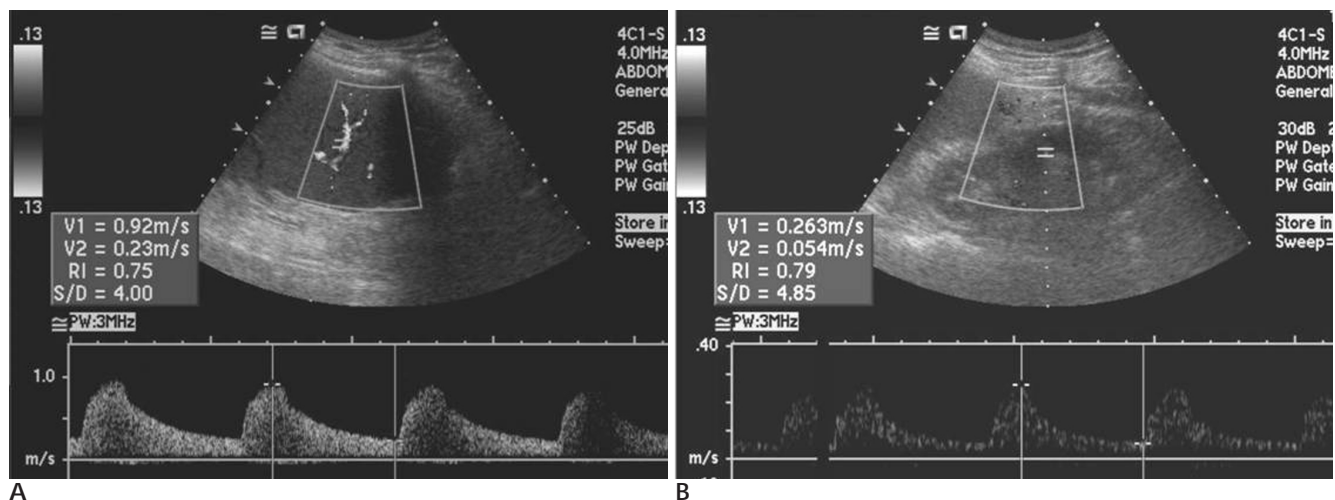


Fig. 1. A 64-year-old man with alcoholic cirrhosis. The patient had a history of hematemesis (triple) with esophageal bleeding. Doppler US shows RIS (A) and RIR (B) measured near the splenic hilum and interlobar artery. In this case, the RIS and RIR values were 0.75 and 0.79, respectively.

Data Analysis

The two groups were compared with respect to the five variables: age, spleen size, Child's score, RIS, and RIR. Correlations between esophageal bleeding episodes and these variables were analyzed. In addition, a correlation between RIS and RIR was analyzed. Multivariate logistic regression analysis was performed to adjust for overlapping variables. A receiver operating characteristic curve (ROCFIT) (University of Chicago—Charles E Metz) was used to identify the cutoff value of the most significant variable for the prediction of bleeding. Sensitivity, specificity, and accuracy for the prediction of bleeding were calculated using the determined cutoff values of the most significant variable. Comparisons between the bleeder and non-bleeder groups were performed using the Student's t-test for unpaired data. *P* values of <0.05 were considered to indicate statistical significance.

Results

The mean values of variables were higher in bleeders than in non-bleeders (60.1 ± 8.6 vs. 55.8 ± 5.1 for age, $p > 0.05$; 14.3 ± 3.1 cm vs. 11.9 ± 2.7 for spleen size; 7.0 ± 1.9 vs. 5.8 ± 1.1 for Child's score; 0.71 ± 0.06 vs. 0.66 ± 0.07 for RIS; 0.73 ± 0.06 vs. 0.67 ± 0.04 for RIR, respectively; $p < 0.05$) (see Table 1). With the exception of age, four variables significantly correlated with bleeding ($r = 0.43$ for spleen size; $r = 0.36$ for Child's score; $r = 0.37$ for RIS; $p < 0.05$, respectively; $r = 0.63$ for RIR, $p < 0.01$). The correlation coefficient between RIS and RIR was 0.78 ($p < 0.01$). Of the variables examined, only RIR was found to significantly predict bleeding (adjusted Odds ratio = 19.9; 95% confidence interval: 1.3 - 306.0, $p < 0.05$) when RIR was more than 0.7 (see Table 2). RIR had a sensitivity of 88.3%, a specificity of 75.0%, and an accuracy of 81.8% at a cutoff value of 0.70 for the prediction of bleeding.

Table 1. The Mean Values of Variables in Bleeders and Non-bleeders

	Bleeders	Non-bleeders	<i>p</i> -value
Age (years)	60.1 ± 8.6	55.8 ± 5.1	0.093
Spleen size (cm)	14.3 ± 3.1	11.9 ± 2.7	0.024
Child score	7.0 ± 1.9	5.8 ± 1.1	0.027
RIS	0.71 ± 0.06	0.66 ± 0.07	0.034
RIR	0.73 ± 0.06	0.67 ± 0.04	0.000

Note. 1. RIS = resistive index of splenic artery, RIR = resistive index of renal artery

2. Only RIR is a significant variable for bleeders (adjusted Odds ratio = 19.9; 95% confidence interval: 1.3 - 306.0, $p < 0.05$)

Table 2. Results of Logistic Regress Analysis for Detection of Bleeders

	<i>p</i> -value	aOR (95.0% CI)
Age (years)	0.017	0.752
Spleen size (cm)	0.175	0.323
Child score	0.632	0.055
RIS (0.7 >)		1.000
(0.7)	0.051	0.969
RIR (0.7 >)		1.000
(0.7)	2.991	0.032
		19.911 (1.296 - 306.003)

Note. 1. aOR = adjusted Odds ratio

2. = standardized regression coefficient

3. CI = confidence interval

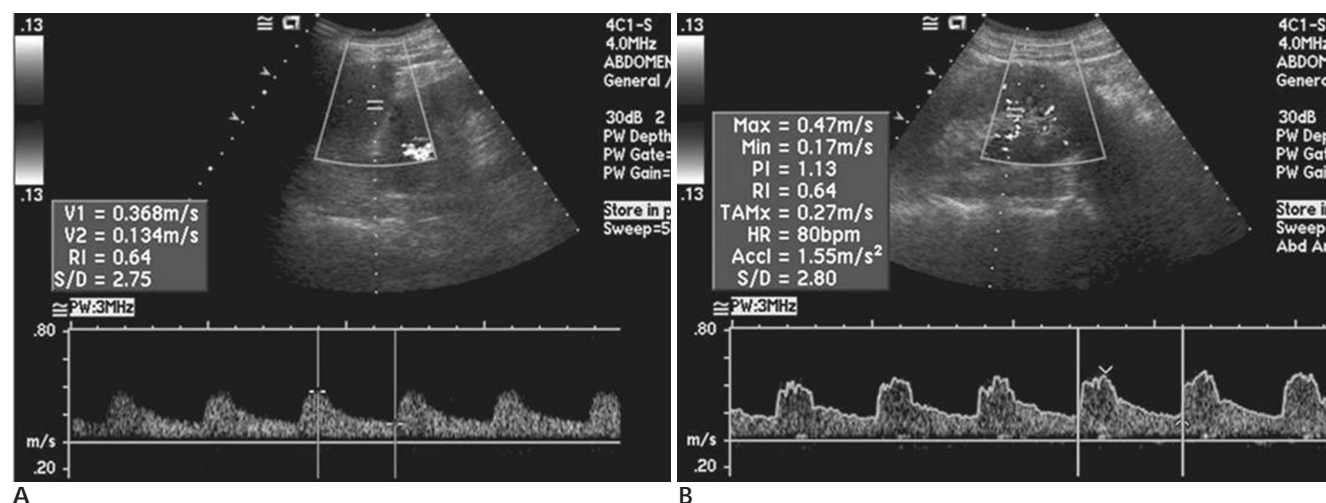


Fig. 2. A 66-year-old man with alcoholic cirrhosis. The patient had no history of hematemesis. RIS (A) and RIR (B) were 0.64 and 0.64 respectively, which were significantly lower than the values associated with variceal bleeding (see Figure 1).

Discussion

A reason for the high incidence of variceal bleeding observed in patients with alcoholic cirrhosis is not clear. However, one study has suggested that the clinical and anatomical features of the major forms of chronic liver disease may explain a high incidence of variceal bleeding (5). This anatomic study showed that portal hypertension in cirrhosis (micronodular or venocentric) is higher than in macronodular cirrhosis. Indeed, hepatic injury in alcoholic cirrhosis is most severe in Rappaport zone 3, near the terminal hepatic venule (6). The hemodynamic sequelae of this injury are similar to those observed in patients with hepatic vein occlusion; if this occlusion is severe enough, portal hypertension with ascites and esophageal varices can develop in the absence of cirrhosis (7). Moreover, oral alcohol consumption increases portal pressure and collateral blood flow in patients with alcohol-induced cirrhosis. These findings suggest that even moderate alcohol consumption worsens portal-hypertensive syndrome, and therefore, may increase the risk of variceal bleeding in patients with alcohol-induced cirrhosis (8).

Much effort has been made to define the risk factors for variceal bleeding. The most frequently used index is that proposed by the North Italian Endoscopic Club (NIEC index), which involves classifying patients into different groups based on predicted 1-year bleeding risks (1). However, the predictive power of this index is far from satisfactory, although it may be improved by incorporating additional parameters related to portal hypertension (i.e., spleen size, platelet count, and hepatic vein pressure gradient (HVPG) measurements). The noninvasive assessment of portal hemodynamics by Doppler ultrasound scans has also received some attention. A summary of the ultrasonographic changes that have been reported to be predictive for variceal bleeding include portal vein enlargement, portal flow reduction, an increased collateral circulation, or the presence of ascites (2, 3). However, assessments of blood flow velocity and volume are unreliable because of low inter-observer and inter-equipment reproducibility. Nevertheless, an accurate identification of patients with a high risk of bleeding would be useful for selecting candidates for prophylactic treatment. To achieve this goal, we evaluated two Doppler ultrasound indices (RIS and RIR) to detect potential bleeding in patients with alcoholic cirrhosis.

In previous studies, RIS has been well correlated with transhepatic portal pressure ($r > 0.8$) (4), and RIS values were found to be higher in patients with varices and in patients with decompensated cirrhosis (4, 9). The highest accuracy for a diagnosis of portal hypertension was achieved using RIS at a cut-off value of 0.6, and this appeared to be the most favorable parameter for clinical practice (10). These studies show that RIS is increased in cirrhotic patients, and it appears that in cirrhotic patients RIS reflects portal vein flow resistance; moreover, this is supported by the observation that RIS is reduced after surgical decompression of the splenic venous system (11). The finding that RIS is elevated in liver cirrhosis patients is interesting from a pathophysiologic standpoint (12, 13). The spleen is located "upstream" with respect to the portal system and may well reflect portal system changes. In addition, it has been shown that bleeding occurs only if the hepatic vein pressure gradient (HVPG) is above a threshold of 12 mmHg (14). However, above this threshold, there is no close relation between HVPG and the risk of bleeding. Clearly, many patients with markedly elevated portal pressures do not bleed from the varices (14). Therefore, a high-pressure gradient is necessary, but is not necessarily sufficient for the rupture of the esophageal varices.

In addition to portal pressure, the amount of blood flow through the gastroesophageal collaterals is believed to be another important factor in the formation and progressive dilatation of the varices (15). Increased portal venous inflow (which is equivalent to the sum of portal and collateral blood flow) is not only an important contributor to the maintenance and worsening of portal pressure elevation but also to hyperdynamic circulation. The most favored theory considers that renal vasoconstriction is the consequence of underfilling the systemic arterial circulation secondary to marked vasodilatation of the splanchnic circulation (15). As increased portal venous inflow is associated the hyperdynamic circulation, increased RIR may be the indirect indicator of a hyperdynamic circulation when there is splanchnic arterial vasodilatation in cirrhosis. Therefore, a high RIR may also be associated with variceal bleeding, as it indicates a worsened hemodynamic status (i.e., a vasodilated state).

In summary, portal hypertension and increased portal venous inflow were found to be the two main factors associated with esophageal varices bleeding. The former is associated with RIS, whereas the later is associated with RIR secondary to a reduction in effective volume, which results in a hyperdynamic circulation. Although these

two indicators are closely related ($r=0.78$; between RIS and RIR), they have different meanings. Thus, we evaluated RIS and RIR separately as indicators of portal hypertension and hyperdynamic circulation, respectively.

In agreement with our expectations, significant differences and correlations were found between the spleen sizes, Child's scores, and the RIR and RIS values of bleeders and non-bleeders in our alcoholic cirrhosis patients. However, adjusted multivariate logistic regression analysis identified RIR alone a significant predictor of bleeding (adjusted odds ratio: 19.9) when the value of RIR was more than 0.7. The reason why only RIR was associated with bleeding is not clear. We can speculate that progressive dilatation of esophageal varices seems to be a chronic homeostatic response to a chronic increase in portal pressure and blood flow. The formation and dilatation of varices seems to relieve portal pressure and may provide a channel for replenishing a reduced effective volume. Under stable conditions, the risk for variceal rupture appears to be relatively low, as varices are the direct result of a chronic adaptive process in cirrhotic patients. However, any condition that results in a rapid increase in portal flow above baseline may increase the risk of variceal bleeding. Therefore, a high RIR, indicating a hyperdynamic circulation, may be more significant than a high RIS in terms of predicting bleeding in patients with a high basal portal pressure. The significance of this hemodynamic factor is supported by findings that bacterial infection is a significant prognostic indicator of a failure to control bleeding (16). Because sepsis is associated with a hyperdynamic circulation, it is not surprising that bacterial infection is frequently diagnosed in cirrhotic patients with variceal hemorrhage. Additional support is provided by the observation that abstinence from alcohol may result in the regression or even the disappearance of varices (14). Thus, RIR may be used as a hemodynamic indicator for the assessment of the risk of variceal bleeding in clinical practice.

This study has several limitations. The first concerns the age distribution of our study group. In this study, age was not found to be correlated with bleeding. Thus, there is a small possibility that age affected our results.. Second, our study was limited to patients with cirrhosis caused entirely by alcohol abuse, and only patients with relatively low Child-Pugh scores were included. Thus, further Doppler studies are required on liver cirrhosis with various etiologies and Child's grades. The third limitation concerns the lack of a pathologic confirmation

of cirrhosis in most patients, as liver biopsies were not obtained. Fourth, the prediction of variceal bleeding based on Doppler parameters was found to be sensitive and specific in terms of predicting bleeders. However, given a diagnostic accuracy of nearly 75%, the clinical consequences using RIR in our study should be reliably evaluated before its use is accepted in clinical practice.

In conclusion, a high RIR appears to be associated with esophageal variceal bleeding in patients with alcoholic liver cirrhosis. We suggest that RIR is a useful predictor of variceal bleeding, and that it should be used clinically to decide whether a patient is to receive prophylactic therapy.

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