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Original Article

Radiological score for hemorrhage in the patients with portal hypertension

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Abstract: Goal: To analyze the risk factors from radiological indices for hemorrhage in the patients with portal hypertension and weight risk factors. Method: We retrospectively analyzed all cases of portal hypertension with hepatitis B from June 2008 to June 2014 in Nanjing Drum Tower hospital. Patients with hepatocellular carcinoma, portal vein thrombosis, or portal hypertension with other causes, such as autoimmune hepatitis, pancreatitis, or hematological diseases were excluded. Results: Ninety-eight patients were recruited and divided into hemorrhage and non-hemorrhage groups. There were no statistical differences in clinical indexes such as age, prothrombin time, serum albumin, serum creatinine, serum sodium, hemameba, and blood platelet count. However, the differences were statistically significant in total bilirubin, hemoglobin, and liver function with the *p* values of 0.023, 0.000, and 0.039 respectively. For radiological indices, hemorrhage was correlated with diameter of inferior mesenteric vein (P=0.0528), posterior gastric vein (P=0.0283), and esophageal varices scores (P=0.0221). Logistic procedure was used to construct the model with stepwise selection and finally inferior mesenteric vein, posterior gastric vein, esophageal varices, and short gastric vein were enrolled into the model. These veins were scored according to the diameters and the rates of hemorrhage were increased with the score. We then validated the model with 26 patents from July 2014 to December 2014. The AUC value was 0.8849 in ROC curves for this radiological model. Conclusions: A risk model was constructed including inferior mesenteric vein, esophageal varices, posterior gastric vein, and short gastric vein. This radiological scoring model may be a valuable indicator for hemorrhage of portal hypertension.

Keywords: Portal hypertension, radiological, hemorrhage, risk assessment, risk factors

Introduction

Portal hypertension is resulted from increased resistance to portal vein blood flow into the liver and is usually caused by the scarring process of cirrhosis. The complications of portal hypertension include variceal hemorrhage, ascites, and portosystemic encephalopathy and so on. Hemorrhage from esophageal or gastric varices is a major factor for prognosis. Therefore, it is important to identify the patients with high risk for bleeding [1].

Hepatic venous pressure gradient (HVPG) is the best predictor of hemorrhage in patients with portal hypertension; however, HVPG measurement is an invasive procedure, which is not readily available in clinical practice, and its cost-effectiveness has been also questioned [2]. Moreover, the clinical utility of repeated monitoring HVPG after pharmacological therapy has not been established [3]. Some endoscopic and imaging-based methods for the assessment of portal haemodynamics and risk of variceal bleeding appear promising [4-7]. These techniques have the potential to complement HVPG in clinical practice, but currently are in limited use. Further studies are needed to confirm the low interobserver variability and the validity of these techniques.

We aimed to analyze the risk factors with radiological indices for hemorrhage in the patients with portal hypertension and to calculate the weight of risk factors.

Table 1. Comparison of the clinical and radiological indexes between hemorrhage and non-hemorrhage groups

Indexes	Hemorrhage group	Non-hemorrhage group	*P* value
Age (years)	49.88±9.88	53.93±13.31	0.077
Total bilirubin (umol/L)	23.33±14.32	44.66±86.23	0.023
Prothrombin time (s)	14.83±2.40	15.01±2.36	0.684
Serum albumin (g/L)	34.55±4.72	33.63±5.16	0.516
Serum creatinine (mmol/L)	62.07±25.60	57.88±15.05	0.535
Serum sodium (mmol/L)	141.01±2.92	140.46±3.56	0.535
Serum hemameba ($10^{\wedge}9$/L)	3.85±5.88	3.43±2.80	0.903
Hemoglobin (g/L)	85.47±19.50	108.74±27.38	0.000
Blood platelet count ($10^{\wedge}9$/L)	71.55±50.83	67.15±50.49	0.465
Liver function			0.039
Child-pough (A)	15	28	
Child-pough (B)	21	12	
Child-pough (C)	5	4	

Materials and methods

Clinical setting and patient selection

We reviewed all cases of portal hypertension with hepatitis B in the record room files from June 2008 to June 2014. Patients with hepatocellular carcinoma, portal vein thrombosis, or portal hypertension with other causes, such as autoimmune hepatitis, pancreatitis, or hematological diseases were excluded. The patients were divided into hemorrhage and non-hemorrhage groups. This study was approved by the IRB of The Affiliated Drum Tower Hospital, Medical School of Nanjing University. The written informed consents for participation in the study were obtained from all participants. We then reviewed the clinical and radiological data. The clinical indices included age, gender, hepatic encephalopathy, ascites, total bilirubin, prothrombin time, serum albumin, serum creatinine, Child-pough classification, serum sodium, hemoglobin, hemameba count, and blood platelet count. The radiological indices included spleen index, diameters of portal vein, superior mesenteric vein, inferior mesenteric vein, splenic vein, venae parumbilicales, coronary vein, spleen kidney shunt, short gastric vein, posterior gastric vein, esophageal vein score and azygos vein. The radiological examinations including computed tomography (CT) and magnetic resonance imaging (MRI) were taken on admission. All examinations were carried out with plain and enhanced with the slice spacing of 5 mm. The radiological indices were measured by two specialist physicians and the average values were used.

Spleen index (SI)

The spleen longitudinal diameter, transverse diameter (through the spleen door) in the largest level of CT and the height of spleen were measured. The SI was the product of the above three (SI=longitudinal diameter* transverse diameter* height) [8].

Esophageal varices score

Esophageal varices score is categorized into 3 groups as follows: Score 1: 1 varix less than 5 mm in diameter detected on the inner surface of the esophagus; Score 2: several varices less than 5 mm in diameter detected on the inner surface of the esophagus; Score 3: 1 varix 5 mm or greater in diameter, or varices occupying more than half the circumference of the esophagus [9].

Measurement of free portal vein pressure (FPP)

Separate splenic vein, right gastroepiploic vein or superior mesenteric vein and insert 4F-6F catheter within the portal venous trunk. Pressure monitor was connected to measure FPP.

Statistical analysis

For comparisons, the Chi-squared test, Fisher's exact test, one-way analysis of variance, and two-tailed student *t* test were performed as appropriate. And the correlation was analyzed with spearman method. Multivariate regression models were fitted to identify independent factors related to hemorrhage adjusted for competing risk, and only variables with $P<0.2$ were retained for multivariate analysis. Results were expressed as hazard ratio (HR) with 95% CI. *P* value of less than 0.05 was considered to be statistically significant. All tests were two sided. Data analysis was done with SAS Version 12.0 software (SPSS Inc, Chicago, IL).

Table 2. Radiological score for hemorrhage and non-hemorrhage groups

Radiological indexes	Criteria (cm)	Hemorrhage (Num)	Non-hemorrhage (Num)	*P* value
Portal vein	<1.3	13	11	
	1.3-1.8	24	20	
	>1.8	20	10	0.5258
Superior mesenteric vein	<0.8	12	13	
	0.8-1.1	25	14	
	>1.1	20	14	0.4421
Inferior mesenteric vein	<0.4	10	15	
	0.4-0.6	34	22	
	>0.6	13	4	0.0528
Splenic vein	<0.9	9	10	
	0.9-1.3	35	19	
	>1.3	13	12	0.3195
Venae parumbilicales	<0.2	19	19	
	0.2-0.4	24	14	
	>0.4	14	8	0.4272
Coronary vein	<0.2	4	3	
	0.2-0.4	44	29	
	>0.4	9	9	0.7299
Spleen kidney shunt	<0.3	43	30	
	0.3-0.6	8	8	
	>0.6	6	3	0.697
Posterior gastric vein	<0.2	18	22	
	≥0.2	39	19	0.0283
Short gastric vein	<0.2	30	15	
	≥0.2	27	26	0.1159
Azygos vein	<0.4	11	6	
	0.4-0.6	25	23	
	>0.6	21	12	0.4881
Esophageal varices		0	0	
		15	20	
		42	21	0.0221
Spleen index (cm^3)		288.91±158.47	308.89±171.22	0.553

Cutoff was validated according to 25, 50, and 75 percentiles.

Results

Clinical characteristics of the patients

Ninety-eight patients were screened (55 men and 43 women, ages ranging from 22 to 76 years, with mean age 51.6 years). Fifty seven patients were assigned into hemorrhage group and 41 patients were allocated into non-hemorrhage group. We analyzed the clinical indexes between hemorrhage and non-hemorrhage groups, and found that there were no statistical differences in clinical indexes such as age, prothrombin time, serum albumin, serum creatinine, serum sodium, hemameba, and blood platelet count (**Table 1**). However, the differences were statistically significant in total bilirubin, hemoglobin, and liver function with the *p* values of 0.023, 0.000, and 0.039 respectively.

Single risk factor for hemorrhage in the patients with portal hypertension

We evaluated the radiological indexes such as diameter of portal vein, superior mesenteric vein, splenic vein, venae parumbilicales, coronary vein, spleen kidney shunt, and azygos vein. To explore the radiological differences between the two groups, we divided them into different groups according to 25% and 75% cut-off levels or 50% cut-off level in **Table 2**. We found that hemorrhage were correlated with inferior mesenteric vein (P=0.0528), posterior gastric vein (P=0.0283), and esophageal varices (P=0.0221), while no correlation with portal vein, superior mesenteric vein, splenic vein, venae parumbilicales, coronary vein, spleen kidney shunt, short gastric vein, and azygos vein.

Multiple risk factors for hemorrhage in the patients with portal hypertension

Logistic procedure was used to construct the model with stepwise selection. Finally, inferior mesenteric vein (P=0.0528), posterior gastric vein (P=0.0283), esophageal varices (P=0.0221) and short gastric vein (P=0.1159) were enrolled into the model. The odds ratio estimates were summarized in **Table 3**. All *p*

Table 3. Multiple logistic aggression analysis in the model

	Score Chi-Square	Pr>ChiSq	Point estimate	95% wald confidence limits
Inferior mesenteric vein	5.8213	0.0158	0.332	(0.157-0.703)
Esophageal varices	5.9419	0.0148	0.341	(0.135-0.861)
Posterior gastric vein	4.9608	0.0259	0.339	(0.861-0.132)
Short gastric vein	5.1617	0.0231	0.308	(0.120-0.792)

Table 4. Scale rule of the selected radiological indexes

Radiologaical indexes	Criteria (cm)	Score
Inferior mesenteric vein	>0.6	1
	0.4-0.6	2
	<0.4	3
Posterior gastric vein	<0.2	1
	≥0.2	2
Short gastric vein	≥0.2	1
	<0.2	2
Esophageal varices	Score 1	1
	Score 2	2
	Score 3	3

Table 5. The scores of hemorrhage and non-hemorrhage groups

Score	Hemorrhage (Num)	Non-hemorrhage (Num)	Bleeding rate
6	3	12	20%
7	13	16	45%
8	24	11	69%
9	15	2	88%
10	2	0	100%

Table 6. The scores of 26 patients with portal hypertension using our model

Score	Hemorrhage (Num)	Non-hemorrhage (Num)	Bleeding rate
6	3	2	60%
7	4	5	44%
8	4	1	80%
9	4	1	80%
10	2	0	100%

values were less than 0.05 and the point estimates were 0.332, 0.341, 0.339, and 0.308 respectively. Therefore, inferior mesenteric vein, posterior gastric vein, esophageal varices and short gastric vein were scored according to the diameters (**Table 4**). The possibility of hemorrhage increased to 20%, 45%, 69%, 88%, and 100% with the score from 6 to 10, respectively (P=0.0004) (**Table 5**).

Model validation

Furthermore, we retrospectively evaluated the patients with portal hypertension from July 2014 to December 2014 using our model. We screened a total of 26 patients and the scores were summarized in **Table 6**. The result showed that the bleeding rates of score 6, 7, 8, 9, and 10 were 60%, 44%, 80%, 80%, and 100% respectively. We also plotted the ROC curves of radiological score model to predict hemorrhage risk of portal hypertension with the AUC of 0.8849 (**Figure 1**).

Radiological indexes are better than FPP to predict hemorrhage

Among the studied patients, 36 cases were tested for FPP. We analyzed the FPP between hemorrhage and non-hemorrhage groups and found that there was no statistical difference with the *p* value of 0.849. We then analyzed the correlation between the model scores and FPP, and found that the correlation coefficient and *p* value were 0.019 and 0.914 respectively.

Discussion

Our study showed that inferior mesenteric vein, esophageal varices, posterior gastric vein, and short gastric vein were correlated with hemorrhage of portal hypertension. For inferior mesenteric vein and short gastric vein, the smaller the diameters, the higher hemorrhage rates were. While for esophageal varices and posterior gastric vein, the hemorrhage rate was proportional to the diameter. To better assess bleeding risk, we built a prediction model with the four veins and graded these veins according to their diameters. We found that the scores were form 4 to 10 with a significant phenomenon that the hemorrhage risk increased with the score. Our study showed that this radiological scoring model may be a valuable indicator for hemorrhage of portal hypertension.

The value of radiological examination in portal hypertension had been widely studied. In the late 1990s, researchers had found that the computerized tomography (CT) could demon-

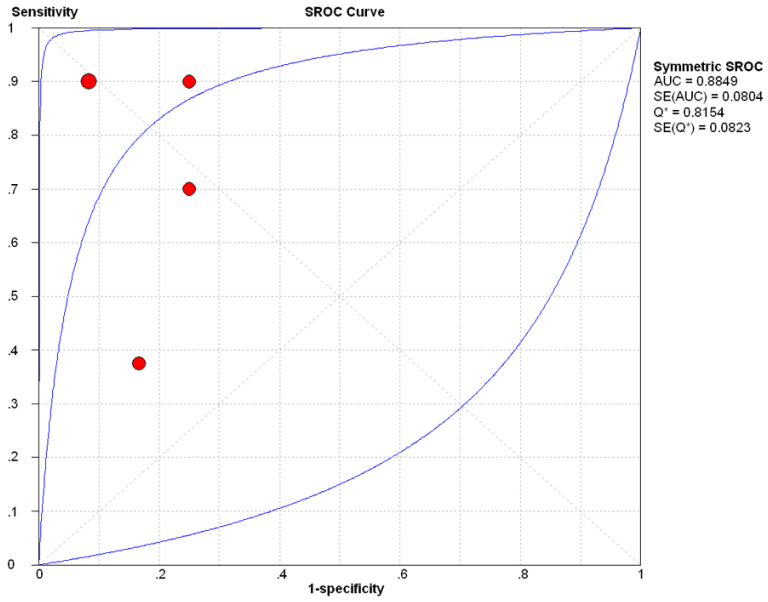

Figure 1. ROC curves of radiological score model for predicting hemorrhage risk of portal hypertension with the AUC of 0.8849.

strate superficial and deep varices, assessed the patency of the extrahepatic portal system, and evaluated other complications including ascites, hepatic statosis, hemochromatosis, and hepatocellcular carcinoma [10]. Recently, the researches of radiology are focused on evaluating of esophageal varices and predicting relapse of varices after treatment. It was concluded from a study to evaluate the performance of liver CT in the detection and grading of esophageal varices in cirrhotic patients that liver CT was useful for the detection and grading of esophageal varices and a diameter of 3 mm might be an appropriate screening threshold for large clinically significant varices [11]. Mifune et al. found that multidetector-row CT (MDCT) was useful in the evaluation of esophageal varices for predicting a risk of hemorrhage [12]. Then, Kodama et al. assessed the relationship between the hemodynamic changes in portosystemic collaterals and the prognosis of patients with esophageal varices after endoscopic injection sclerotherapy using multiplanar reconstruction (MPR) MDCT images. The result showed that MPR MDCT images on portosystemic collaterals could accurately predict relapse of esophageal varices after endoscopic injection sclerotherapy [13]. However, the assessment was based only on esophageal varices. There is no study on the radiological model for predicting hemorrhage of portal hypertension. As we know, the collateral veins form gradually with portal hypertension. Thus, our study proposed a predicting model through grading the diameters of inferior mesenteric vein, esophageal varices, posterior gastric vein, and short gastric vein, which could predict different bleeding rates of portal hypertension. We also validated the model through 26 patients of portal hypertension. The result was in agreement with our model to a certain extent and the AUC was 0.8849 in ROC curves. The esophageal varices had been studied to be useful in predicting hemorrhage of portal hypertension [12]. However, inferior mesenteric vein, posterior gastric vein, and short gastric vein had never been reported to participate in predicting hemorrhage and our study firstly brought inferior mesenteric vein, posterior gastric vein, and short gastric vein into the evaluating system Nonetheless, the model should be further validated proactively because of the limitation of the number of study cases.

Several studies have evaluated laboratory and/or ultrasonographic findings (usually the platelet count and the size of spleen on transabdominal ultrasound) as surrogate markers for oesophageal varices with the aim of predicting bleeding [14-17]. In 1988, the North Italian Endoscopic Club described a formula to predict bleeding risk based on the Child-Pough class and endoscopic parameters of variceal size and red wale marks [18]. To date, none of these tests had become established in clinical practice for this indication or for assessing response to pharmaceutical therapy. Endoscopic ultrasonography (EUS) has also been used in the assessment of portal hypertension. A series of studies have shown that EUS is superior to conventional endoscopy in the diagnosis of varices and can more accurately detect the variceal size. Escorsell et al. used EUS morphological assessment of varices (column radius and volume) combined with simultaneous pressure measurement for risk stratification and the

assessment of drug effect on portal haemodynamics [19]. Miller et al. also found that there was a significant difference (P<0.018) in the sum of the oesophageal variceal cross-sectional surface area between those patients who would experience future variceal bleeding and those who would not [20]. EUS can provide significant information regarding the morphological assessment of varices, but it is not clear whether the EUS appearances of varices alone or combined with simultaneous intravariceal pressure measurements would permit accurate risk stratification in a prognostic model and predict bleeding risk [21].

Our study proposed a radiological model, which could predict accurate risk stratification for hemorrhage. However, our study is retrospective and the results need to be validated further. Our team will design a prospective study to validate this model. We expect that the model will not only predict bleeding risk, but also guide treatment to give preventive treatment to avoid bleeding for high bleeding risk patients of portal hypertension.

Conclusion

We built a prediction model including inferior mesenteric vein, esophageal varices, posterior gastric vein and short gastric vein, and graded them according to the diameter. We found that the rates of hemorrhage increased with the score. This radiological scoring model may be a valuable indicator for hemorrhage of portal hypertension.

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Disclosure of conflict of interest

None.

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