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Araştırma

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Predictors Of Variceal Rebleeding In Liver Cirrhosis

Sirotik Varis Kanamalarında Tekrar Kanama Belirleyicileri

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ABSTRACT

Aim: Cirrhotic patients with acute variceal bleeding are characterized by a high mortality and rebleeding rate. The aim of this study was to explore predictors of rebleeding in cirrhotic patients.

Methods: Cirrhotic patients who were admitted to the hospital were retrospectively analyzed. Rebleeding was defined as a new onset of hematemesis, hematochezia or melena after endoscopic therapy, and a period of stable vital signs and hemoglobin. Medical records as laboratory data include hemoglobin and platelet level, prothrombin time, creatinine, bilirubin, albumin level, vital signs, need of blood transfusions, comorbidities, medications, clinical findings as presence of ascites and hepatic encephalopathy, and endoscopic findings of varices were recorded and entered a computer-based database. Child-Pugh grade was also calculated and recorded.

Results: 20 patients (21%) with recurrent hemorrhage after control of the variceal bleeding during the six-week follow-up period were included in this study. The level of albumin and hemoglobin in the rebleeding group were significantly lower than those in non-rebleeding group. The mean level of albumin was 2.45 mg/dL (vs. 3.05 mg/dL, p=0.01) and hemoglobin was 7.96 g/dL (vs. 9.92 g/dL, p=0.001). Ascites was seen to be significantly higher in the rebleeding group (50% vs. 14%, p=0.002). After multivariate regression analysis, we found that lower hemoglobin level and Child-Pugh grade were the only independent significant predictors for variceal rebleeding.

Conclusion: Since factors such as the Child-Pugh grade, hypoalbuminemia and presence of ascites are associated with portal hypertension and hepatic failure, we found that lower hemoglobin level and Child-Pugh grade were the only independent significant predictors for variceal rebleeding.

Key Words: Varice, Hemorrhage, Mortality.

ÖZET

Amaç: Sirotik varis kanamaları yüksek mortalite ve tekrar kanama oranları ile karakterizedir. Bu çalışmada tekrar kanama belirleyicilerinin saptanması amaçlanmıştır.

Yöntem: Hastaneye başvuran siroz hastaları retrospektif olarak değerlendirilmiştir. Endoskopik müdahale ve vital bulguların stabil hale gelmesi sonrasında yeni gelişen hematemez, melena, hematokezya bulguları ve hemoglobin düzeyinde düşme görülmesi tekrar kanama olarak tanımlanmıştır. Hastaların hemoglobin ve trombosit düzeyi, protrombin zamanı, kreatinin, bilirubin, albümin düzeyi, vital bulguları, kan transfüzyonu ihtiyacı durumu, komorbiditeleri, ilaçları, asit varlığı ve hepatik ensefalopati varlığı gibi klinik bulguları ve varislerin endoskopik bulguları bilgisayar tabanlı bir veritabanına kaydedilmiştir. Child-Pugh evresi de kaydedilmiştir.

Bulgular: Varis kanamalarının kontrolünden sonraki altı haftalık dönemlerinde tekrarlayan kanaması olan 20 hasta (%21) saptanmıştır. Tekrar kanaması olan grupta albümin ve hemoglobin düzeyi, tekrar kanamayan gruba göre anlamlı derecede düşüktü. Albümin seviyesi (2.45 & 3,05 mg/dl, p=0.01) ve hemoglobin 7.96 & 9.92 g/dl'ydi, p=0.001). Tekrar kanaması olan grupta asit sıklığı, tekrar kanamayan gruba göre anlamlı olarak daha yüksekti (%50 & %14, p=0,002). Çok değişkenli regresyon analizden sonra, düşük hemoglobin seviyesi ve Child-Pugh evresinin varislerde tekrar kanama için tek bağımsız anlamlı risk faktörleri olduğu saptanmıştır.

Sonuç: Child-Pugh evresi, hipoalbüminemi ve asit varlığı gibi faktörler portal hipertansiyon ve karaciğer yetmezliği ile ilişkili olduğundan, düşük hemoglobin düzeyi ve Child-Pugh evresinin tekrarlayan varis kanaması için tek bağımsız anlamlı risk faktörleri olduğu saptanmıştır.

Anahtar Kelimeler: Varis, Kanama, Mortalite

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Introduction

Variceal bleeding is a frequent and severe complication observed in cirrhosis [1]. Cirrhotic patients with acute variceal bleeding are characterized by a high mortality and rebleeding rate [2]. Although there are new therapeutic options, variceal rebleeding still occurs in a high rate, with some studies showing 50% rebleeding rate [1]. This high rate of variceal rebleeding is associated with increased morbidity, length of hospital stay and mortality in cirrhotic patients [3]. In a study by Habib et al., over 60 years of age, renal failure, alcoholic cirrhosis, thrombocytopenia, hemoglobin lower than 8 g/dL at presentation, presence of ascites and encephalopathy, were found to be related with rebleeding [4]. The aim of this study was to explore predictors of rebleeding in cirrhotic patients.

Materials and Methods

Study Design and Data Collection

Cirrhotic patients who were admitted to Osmangazi University Hospital in Eskisehir due to variceal bleeding between 2013 and 2017, were retrospectively analyzed. Ethic approval was obtained from the Ethics Committee of Medicine Faculty with the decision date 13.02.2017 and number 6. The inclusion criterion was history of variceal bleeding with cirrhotic etiology. The exclusion criteria included non-cirrhotic etiology and patients with incomplete clinical data. Rebleeding was defined as a new onset of hematemesis, hematochezia or melena after endoscopic therapy, a period of stable vital signs and hemoglobin. Medical records as laboratory data include hemoglobin and platelet level, prothrombin time, creatinine, bilirubin, albumin level, vital signs, need of blood transfusions, comorbidities, medications, clinical findings as presence of ascites and hepatic encephalopathy, as well as endoscopic findings of varices, were recorded and entered a computer-based database. Child-Pugh grade was also calculated and recorded.

Statistical Analysis

Statistical analysis was performed with the IBM SPSS, version 21 (IBM, NY, USA). Normality test was performed with the Shapiro-Wilk test. Variables were compared using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. Univariate logistic regression analysis was done first for each predictor to identify the significant predictor and then, the most independent significant predictors were evaluated using the multivariable logistic regression analysis by entering all the previously identified significant predictors simultaneously, with a stepwise backward strategy. A P value below 0.05 was considered statistically significant and a 95% confidence interval were calculated for measures of association.

Results

A total of 134 patients with cirrhosis and variceal bleeding were enrolled in this study, in which 38 patients whose clinical data was incomplete were excluded. Of the remaining 96 patients, 20 (21%) with recurrent hemorrhage after control of the variceal bleeding during the six-week follow-up period, were assigned to the rebleeding group. Table 1 of our results shows the participants' demographic criteria, the different clinical presentations of variceal bleeding, laboratory and other parameters related with liver dysfunction and the endoscopic variceal signs.

There were no significant differences between two groups (rebleeding & non-rebleeding group) in mean age (59 vs. 58 years, p=0.87), gender (female %) (40% vs. 36.8%, p=0.79), bilirubin level (3.1 vs. 1.7, p=0.07), platelet count (148 vs. 132×10^9/L, p=0.58) and endoscopic findings (p=0.22). The level of albumin and hemoglobin in the rebleeding group were significantly lower than those in the nonrebleeding group. The level of albumin was 2.45 mg/dl (vs. 3.05 mg/dl, p=0.01) and hemoglobin were 7.96 g/dl (vs. 9.92 g/dl, p=0.001). The frequency of ascites in the rebleeding group were significantly higher than those in the non-rebleeding groups (50% vs. 14%, p=0.002).

In the logistic regression analysis model, two variables were positively correlated with rebleeding: Child-Pugh grade C (OR=2.587, 95% CI 1.197–5.594) (compared with Child-Pugh grade A-B) and presence of ascites (OR=5.333, 95%CI 1.826 -15.574). The albumin level (OR=0.224, 95% CI 0.091-0.554) and hemoglobin level (OR=0.676, 95% CI 0.517–0.808) were negatively correlated with rebleeding of the cirrhotic inpatients. After multivariate analysis, we found that a lower hemoglobin level and the Child-Pugh grade were the only independent significant predictors for variceal rebleeding. This data is shown in Table 2.

Discussion

Cirrhosis is associated with high morbidity and mortality due to complications such as hepatic insufficiency and portal hypertension, and such as ascites, hepatic encephalopathy and variceal bleeding and survival is shortened when decompensation develops [5]. Approximately one third of cirrhotic patients with esophageal varices will eventually bleed, and one third of these may die as a result of a variceal hemorrhage [6].

Rebleeding is an important cause of poor prognosis and mortality in variceal bleeding. Therefore, it is important to determine the patients with high risk of rebleeding

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Table 1. Demographic criteria, endoscopic characteristics and laboratory parameters.

		Total n=96		Rebleeding n=20		No rebleeding n=76		Sig.
Demographic criteria								
Age (years)	Mean (SD)	58	(14)	59	(13)	58	(15)	0.87
Sex (Female)	Count (%)	36	(37.5)	8	40%	28	36.8%	0.79
Clinical presentation								
Hematemesis	Count (%)	84	87.5%	20	100%	64	84.2%	0.014
Melena	Count (%)	50	52.1%	11	55%	39	51.3%	0.769
Syncope	Count (%)	10	10.4%	4	20%	6	7.8%	0.142
Liver function test								
Serum albumin mg/dl	Mean (SD)	2.92	(0.69)	2.45	(0.58)	3.05	(0.66)	0.001
Serum bilirubin mg/dl	Mean (SD)	1.99	(2.74)	3.1	(4.4)	1.70	(2.0)	0.07
Prothrombine time(INR)	Median (25-75)	1.40	(1.28-1.60)	1.54	(1.32-1.87)	1.35	(1.27-1.57)	0.46
Child- Pugh Grade								
Grade A	Count (%)	45	46.9%	7	35%	38	46.9%	
Grade B	Count (%)	42	43.8%	7	35%	35	43.8%	
Grade C	Count (%)	9	9.4%	6	30%	3	9.4%	0.002
Presence of ascites	Count (%)	22	23%	10	50%	12	16%	0.002
Presence of Encephalopathy	Count (%)	3	3%	1	5%	2	2.6%	0.594
Other parameters								
Hemoglobin (g/dL)	Mean (SD)	9.51	(2.38)	7.96	(1.7)	9.92	(2.3)	0.001
Platelets (×103/mm3)	Mean (SD)	135	(112)	148	(107)	132	(114)	0.58
Serum creatinine (mg/dL)	Median (25-75)	0.85	(0.60-1.16)	0.9	(0.52-1.45)	0.82	(0.6-1.09)	0.78
Endoscopic signs								
Variceal Form								
F1	Count (%)	11	11.5%	1	5%	10	13.2%	
F2	Count (%)	36	37.5%	10	50%	26	34.2%	
F3	Count (%)	48	50%	9	45%	39	51.6%	0.226
Red Color(RC) Sign								
RC +	Count (%)	75	78.1%	14	70%	61	80.2%	
RC–	Count (%)	20	20.8%	6	30%	14	18.5%	0.52

and the factors associated with it in order to decrease the rate of rebreeding and mortality [7]. The rates of rebleeding in the first six-week period were 17% in the study of Krige et al., as well as 28.8% in the Al Freah et al. and 10.7% in the Hobolth et al. studies [8-10]. In the latter, the rate of rebleeding had decreased from 22.2% to 10.7% between the 1980s and 2000s, although this decrease did not reach a statistical significance. The rate of vasoactive drug use was significantly higher in the 2000s [10]. In comparison, the rate of rebleeding in our study was 20%. In previous studies, rate of rebleeding was found to be associated with vasoactive drug use [10], MELD score [11], serum creatinine, albumin and necessity for blood transfusion [7]. However, other studies did not find such an association with the MELD score [7,9] and blood transfusion [9,11]. Child-Pugh score and presence of ascites were not found to be associated with rebleeding in these studies. In our study, the Child-Pugh grade, presence of ascites, lower average hemoglobin and lower average serum albumin at presentation, were found to be associated with rebleeding. However, after the multivariate analysis, only the lower average hemoglobin at presentation and the Child-Pugh grade were independently associated with rebleeding.

Table 2. Univariate logistic regression analysis for the evaluated predictors

	Constant	B	SE	Wald	Sig.	EXP(B)	%95 CI Lower	Upper
Demographic criteria								
Age (years)	-1.499	0.003	0.017	0.026	0.87	1.000	0.969	1.037
Sex	-1.119	-0.134	0.515	0.067	0.79	0.875	0.319	2.399
Liver functions								
Serum albumin mg/dl	2.76	-1.49	0.461	10.49	0.001	0.224	0.091	0.554
Serum bilirubin mg/dl	-1.658	0.146	0.082	3.154	0.076	1.157	0.985	1.358
Prothrombine time (INR)	-1.717	0.241	0.337	0.512	0.474	1.273	0.657	2.466
Child-Pugh Grade	-2.986	0.951	0.393	5.837	0.016	2.587	1.197	5.594
Presence of ascites	-1.856	1.674	0.547	9.373	0.002	5.333	1.826	15.574
Presence of Encephalopathy	-1.360	0.666	1.251	0.284	0.594	1.947	0.168	22.630
Other laboratory parameters								
Serum creatinine mg/dl	-1.230	-0.103	0.368	0.079	0.779	0.902	0.439	1.854
Platelets($x10^3/mm^3$)	-1.488	0.001	0.001	0.307	0.58	1.0	1.0	1.0
Hemoglobin g/dl	2.16	-0.391	0.127	3.43	0.02	0.676	0.517	0.808
Endoscopic parameters								
Variceal form	-6.424	1.347	1.113	1.465	0.226	3.846	0.434	34.064
Red Color Sign	-0.847	-0.641	0.571	1.261	0.261	0.527	0.172	1.612

Limitations

Our study had two limitations, namely that most of our patient populations had Child-Pugh grade A and B, whereas a small group was Child-Pugh grade C. In addition, our study was done retrospectively and had a small patient population. There is now a need for additional studies with large patient cohorts.

Conclusion

Since factors such as Child-Pugh score, hypoalbuminemia and presence of ascites are associated with portal hypertension and hepatic failure, we tried searching other laboratory parameters that may be associated with rebleeding. After univariate and multivariate analysis of other laboratory criteria for our participants, we found that lower hemoglobin level and Child-Pugh grade were the only independent significant predictors for variceal rebleeding.

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Ethics Committee Approval: In this study, national and international ethical rules were observed.

Ethic Board: Ethics Committee of Medicine Faculty of Osmangazi University with the decision dated 13.02.2017 and numbered 6.

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