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Portal hypertensive bleeding independently predicts mortality in patients hospitalized for alcoholic hepatitis with gastrointestinal bleeding

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임상의과학과

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ABSTRACT

Introduction: Gastrointestinal bleeding (GIB) is often accompanied by patients with alcoholic hepatitis (AH). The aims of the present study were 1) to identify the etiologies of GIB in patients hospitalized for AH; 2) to investigate the clinical characteristics and long-term survival outcomes of patients hospitalized for AH according to the presence or absence of GIB; 3) to identify factors associated with long-term mortality.

Methods: A hospital-based, retrospective cohort comprised consecutive patients who were hospitalized for AH between 1999 and 2014. Those patients were dichotomized into two groups: those who experienced GIB once or more (GIB group) and those who never experienced GIB till death or censoring (Non-GIB group). GIB group was dichotomized into another two groups: those whose bleeding focus of the 1st GIB was found to be portal hypertensive bleeding (PHB group) and those of non-portal hypertensive bleeding (Non-PHB group). Clinical characteristics and long-term survival outcomes of patients hospitalized for AH according to the presence or absence of GIB and PHB were investigated. Risk factors for long-term mortality in AH patients were also analyzed using the Cox regression method.

Results: A total of 329 patients hospitalized for AH were included in this study. Among them, 132 patients experienced GIB at admission or during follow up. Of the 132 patients, the most common cause of GIB was esophageal varix. Using the log rank test, GIB group had worse survival outcome compared with Non-GIB group (log rank test, p=0.034). PHB group

had worse survival outcome compared with the Non-PHB group (log rank test, p=0.001). There was no significant difference in survival rate between the Non-PHB group and Non-GIB group. In the multivariable analysis of all AH patients, alcohol dose, ascites, encephalopathy, Maddrey's discriminant function (MDF) and the model for end-stage liver disease (MELD) were associated with mortality. In the multivariable analysis of GIB group, MELD score (HR, 1.094; 95% CI, 1.063-1.127; P<0.001) and the presence of PHB (HR, 2.178; 95% CI, 1.023-4.634; P=0.043) were found to be independently associated with mortality.

Conclusions: Portal hypertensive bleeding and high MELD scores independently predicted worse survival outcomes in AH patients with gastrointestinal bleeding. Therefore, the prompt endoscopic examination may help physicians to stratify the risk of mortality in AH patients with GIB.

Key Words: alcoholic hepatitis, gastrointestinal bleeding, portal hypertension, survival

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INTRODUCTION

Alcoholic liver disease (ALD) is one of the leading causes of advanced liver disease worldwide. ALD has a broad spectrum, including simple steatosis, steatohepatitis, cirrhosis, and acute alcoholic hepatitis.(1)

Alcoholic hepatitis (AH) is an acute clinical syndrome characterized by jaundice and hepatic decompensation caused by chronic excessive alcohol use.(2, 3) Abstinence from alcohol is the cornerstone for recovery. Not all patients with AH require hospitalization or medical treatment, but severe AH is often complicated by acute kidney injury, gastrointestinal bleeding, hepatic failure or infection.(2, 4) Mild cases of AH have a favorable outcome, but severe cases of AH have a high mortality rate.(2, 5)

Several clinical models were developed to predict mortality in AH patients. Maddrey's discriminant function (MDF) is known widely to predict risk of mortality, but MDF has a drawback that it is poorly standardized across different laboratories.(6) The model for end-stage liver disease (MELD), originally derived to assess the short-term prognosis of patients with cirrhosis, is a survival model based on a composite of three laboratory variables; serum creatinine, serum bilirubin and international normalized ratio (INR) for prothrombin time.(7) It has been reported repeatedly that MELD model is useful for predicting mortality in AH patients.(6, 8, 9)

An earlier meta-analysis by Imperiale et al reported that, after excluding subjects with gastrointestinal bleeding (GIB), corticosteroids (CS) reduced mortality in acute AH patients.(10) Since this study by Imperiale et al, the

efficacy of CS has not been evaluated in patients with GIB, which were exclusion criteria in many of the clinical trials.(11) According to various recommendations, CS are indicated for treatment of severe AH in the absence of gastrointestinal bleeding.(2, 3, 11, 12) A recent meta-analysis analyzing data from 418 patients from 5 randomized controlled trials showed that CS significantly improved survival in patients with severe AH.(13) This study provided a strong evidence for the mortality benefit in the treatment of AH. However, in this study by Mathurin et al, whether AH patients with GIB were excluded or not was not clearly stated. To date, no concrete data are available with regard to the efficacy of CS in AH patients with GIB. In a study on the prognosis of AH patients, the association of GIB with mortality has been reported.(3, 14) In a Danish study, half of AH patients had cirrhosis already at the time of AH diagnosis. This study reported that 11% of AH patients with cirrhosis died of variceal bleeding.(15) A study on the mortality of AH showed that gastrointestinal bleeding accounted for 21% of all deaths of AH patients.(4) Although etiologies other than variceal bleeding can also cause gastrointestinal bleeding in AH patients, the clinical outcomes of AH patients with gastrointestinal bleeding has never been evaluated according to specific etiologies of gastrointestinal bleeding. Meta-analysis by Imperiale *et al* did not specify the etiologies of gastrointestinal bleeding.(10)

The aims of the present study were 1) to identify the etiologies of GIB in patients hospitalized for AH; 2) to investigate the clinical characteristics and long-term survival outcomes of patients hospitalized for AH according to the presence or absence of GIB; 3) to identify factors associated with mortality.

METHODS

Study Population

The study protocol was approved by the Institutional Review Board of Seoul National University Boramae Medical Center. We designed a retrospective cohort study that included hospitalized AH patients fulfilling the eligibility criteria at Seoul National University Boramae Medical Center between December 1999 and July 2014. The presence of AH was confirmed via clinical and laboratory criteria as follows: (1) alcohol consumption within 2 months and exceeding 40 g/d for male and 20 g/d for female patients; (2) an aspartate/alanine aminotransferase (AST/ALT) ratio above 1.5 with an AST level above 45 IU/L; (3) a total bilirubin level above 2 mg/dL. These criteria allowed for the inclusion of patients with mild and severe AH. The following patients were excluded : (1) patients with causes of liver disease other than alcohol consumption (i.e., viral hepatitis, autoimmune hepatitis, and drug-induced hepatitis); (2) non-liver malignancies.

Data Collection and Outcome Measurement

Demographic, clinical and laboratory data were obtained by reviewing the electronic medical records. The clinical and laboratory characteristics of patients who were hospitalized for AH were examined. We also analyzed risk factors associated with long-term mortality. All AH patients were dichotomized into two groups: those who experienced GIB once or more after enrollment (GIB group) and those who never experienced GIB till death or censoring (Non-GIB group). In the GIB group, the specific etiologies of

gastrointestinal bleeding were investigated. Clinical findings were compared between GIB group and Non-GIB group. In the comparison between GIB group and Non-GIB group, clinical data on the 1st date of 1st admission were evaluated and the time to death or censoring was calculated from that day. Data for patients who did not die were censored at the date of the last follow up visit. The predictors of mortality were searched among the clinical data on the 1st date of 1st admission. The GIB group was dichotomized into another two groups: those whose bleeding focus of the 1st GIB was found to be portal hypertensive bleeding (PHB group) and those of non-portal hypertensive bleeding (Non-PHB group). Portal hypertensive bleeding (PHB) included esophageal/gastric variceal bleeding or portal hypertensive gastropathy/colopathy bleeding. Bleedings due to gastric ulcer, duodenal ulcer, Mallory-Weiss tear, Dieulafoy's lesion were regarded as non-portal hypertensive bleeding (Non-PHB). Clinical findings were compared between PHB group and Non-PHB group. In the comparison between PHB group and Non-PHB group, clinical data within 24 hours from the bleeding event were evaluated and the time to death or censoring was calculated from the date of 1st bleeding. Gastrointestinal bleeding was defined as evidence of hematemesis/melena/hematochezia or a drop in hemoglobin of 2 g/dL or more from baseline, or the need for a transfusion. Presence or absence of ascites and hepatic encephalopathy were based on physical exam findings described in the electronic medical records at admission. For patients hospitalized more than once for AH in the time period, only the data of 1st admission were included. For patients with more than one episode of GIB in the time period,

only the data of the initial episode were evaluated. The primary endpoint was overall mortality due to any cause during the follow up period. The overall mortality was defined as those who died at any time during the follow up period. Data on the amount of alcohol consumption depended on self-reported information. To avoid inaccuracy of data on the amount of alcohol consumption, nursing charts as well as physicians' medical records were meticulously reviewed. Survival was verified with hospital record.

Statistical Analysis

Descriptive statistics data such as means, SDs, percentages were calculated to characterize the patients. Comparisons between two groups were performed using Student's *t* test for continuous variables and chi-square test or Fisher's exact test for categorical variables. Patient survival was estimated by the Kaplan-Meier method and compared using the log-rank test. The Cox regression analysis was used to identify factors independently associated with survival. In the Cox regression analysis, variables reaching a *P* value<0.1 in univariable analyses were included in the multivariable analysis. The multivariable analysis was performed using a backward stepwise selection method to identify independent predictors associated with mortality. A *P* value <0.05 was considered statistically significant.

RESULTS

Demographic, clinical and laboratory findings of hospitalized AH patients

A total of 332 consecutive hospitalized AH patients were identified with the diagnosis of AH. After excluding 3 patients with non-liver malignancies (1 pancreatic cancer, 1 stomach cancer, and 1 renal cell carcinoma), 329 patients were analyzed in this study. The mean age of these 329 patients was 51.5 years. Male was predominant (89.7%). All of the patients were of Asian ethnicity. 249 (75.7%) had results of hepatic imaging at index admission. Of the 249 patients with radiologic evaluation of liver, 167 (67.1%) had been diagnosed with liver cirrhosis at index admission. Nineteen patients were diagnosed with hepatocellular carcinoma during follow-up. Among the 329 patients, 132 patients (40.1%) experienced GIB (GIB group). Among the 132 cases with GIB, 96 cases (72.7%) were admitted for GIB and 36 cases (27.3%) developed GIB after admission for other causes. 197 (59.9%) patients of 329 did not experience GIB, and were hospitalized for causes other than GIB (Non-GIB group). The demographic, clinical and laboratory findings were compared between GIB group and Non-GIB group. (Table 1) There were no significant differences in clinical parameters between GIB group and Non-GIB group. Table 2 shows the comparison of demographic, clinical and laboratory findings between PHB group and Non-PHB group. The causes of liver-related death in AH patients included hepatic failure, hepatorenal syndrome, gastrointestinal bleeding and infection. Other causes included

sudden cardiac arrest, intracerebral hemorrhage, subdural hematoma, asphyxia.

Causes of gastrointestinal bleeding

The most common cause of GIB in hospitalized AH patients was esophageal varix. Other causes were portal hypertensive gastropathy/colopathy, gastric/duodenal ulcer, Mallory-Weiss tear, Dieulafoy's lesion and gastric varix. The hemostatic procedures or medical therapies performed were also presented. (Table 3)

Survival outcomes and comparison between groups

Of the 329 AH patients, 120 (36.5%) died. Median observation time (from the 1st date of 1st admission) was 678 days (range 1-5534 d). Of the 132 patients who experienced GIB (GIB group), 64 (48.5%) died. Of the 197 patients who never experienced GIB (Non-GIB group), 56 (28.4%) died (P <0.001). Of the 75 patients who were admitted for GIB at 1st admission, 31 (41.3%) died. Of the 254 patients who were admitted for causes other than GIB at 1st admission, 89 (35.0%) died (P =0.320). (Table 4) GIB group showed worse survival outcome compared with Non-GIB group (log rank test, P =0.034, Fig 1) PHB group had worse survival outcome compared with the Non-PHB group (log rank test, P =0.001, Fig 2). There was no significant difference in survival rate between the Non-PHB group and Non-GIB group. (Fig 3)

Risk Factors for Mortality in Hospitalized AH Patients

In the univariable Cox regression analysis of the total 329 patients, 8 variables were associated with survival. Because prothrombin time, creatinine and bilirubin are the components of MDF or MELD, they were excluded from the

subsequent multivariable analysis to avoid bias related to the effect of colinearity. In the multivariable analysis, alcohol dose, ascites, encephalopathy, MDF and MELD were associated with mortality. (Table 5) In the univariable Cox regression analysis of GIB group, 9 variables were associated with mortality. Likewise, prothrombin time, creatinine and bilirubin were excluded from the subsequent multivariable analysis. In the multivariable Cox regression analysis of GIB group, a backward elimination procedure was performed. MELD score ($p<0.001$) and the presence of PHB ($p=0.043$) were found to be independently associated with mortality. (Table 6)

DISCUSSION

To our knowledge, this study is the first study to investigate the clinical characteristics and long-term survival outcomes of patients hospitalized for AH according to the presence or absence of GIB. We sought to investigate the clinical characteristics and long-term survival outcomes of AH patients according to the presence or absence of GIB. Thus, comparison of clinical parameters at index hospitalization between GIB group and Non-GIB group was performed. Table 1 shows there were no significant differences between GIB group and Non-GIB group. GIB group had a tendency to ingest more alcohol than Non-GIB group, but without statistical significance. Prothrombin time of GIB group had a tendency to be longer than Non-GIB group, without statistical significance.

Portal hypertension is related to hepatic decompensation and it is speculated that subjects with portal hypertension have poor prognosis or high risk of recurrent GIB. However, to date, the clinical outcomes of AH patients with GIB has never been evaluated according to specific etiologies of gastrointestinal bleeding. In this regard, we performed the comparison of clinical findings at index hospitalization between PHB group and Non-PHB group. Table 2 shows PHB group more frequently had ascites, transfusion of packed cells, and worse prothrombin time, MDF and MELD score than Non-PHB group.

In our study, causes of death were diverse. The majority of deaths in AH patients were liver-related including hepatic failure, hepatorenal syndrome,

gastrointestinal bleeding and infection. However, not a small portion (16.7%, 20/120) of them died of seemingly liver-unrelated causes such as intracerebral hemorrhage, subdural hemorrhage or sudden arrest. (Table 7) Subjects who were found dead are thought to have the possibility of sepsis due to infection, so we could not assure that their cause of death was not liver-related. Likewise, in those who died of intracerebral hemorrhage, subdural hematoma, the cause of death can be attributed to coagulation abnormality due to hepatic decompensation. Asphyxia can also be attributed to dysfunction in deglutition related to hepatic encephalopathy. Therefore, instead of liver-related mortality, we calculated overall mortality regardless of the specific cause of death, with exception of extrahepatic malignancies. In our study, 12.5% (15/120) were found dead in a state of cardiac arrest of unknown cause. This result concurs with Orntoft et al's study where 16% were found dead.(15) The majority of the deceased AH patients have multiple contributing causes of death, and Orntoft et al hierarchically categorized the causes of death. Indeed, it is difficult to determine only one cause of death in the deceased AH patients. In a report by Yu et al, the three main causes of death in AH were hepatic failure, GIB and infection.(4)

As shown in table 3, the primary cause of GIB in hospitalized AH patients was esophageal varix. PHB occupied 75% of the GIB. More than 20% of the GIB in hospitalized AH patients was due to Non-PHB.

Non-GIB group (patients who never experienced GIB till death or censoring) survived more than GIB group (patients who experienced GIB) as shown in table 4. However, when the presence of GIB is restricted to index

hospitalization, the group with GIB at index hospitalization and those without GIB showed no difference in survival (P=0.320). This can be attributed to the small number of patients who manifested as GIB. The Kaplan-Meier curves showing survival differences between groups were presented in figures. GIB group showed worse survival outcome than Non-GIB group (Fig 1). PHB group had worse survival outcome than Non-PHB group (Fig 2). And survival rate was not significantly different between Non-PHB group and Non-GIB group (Fig 3). These findings may imply that mortality of GIB group is mainly attributed to PHB and that Non-PHB has little association with the survival of AH patients. The survival curves of AH patients according to GIB or PHB have not been presented in previous studies. A study by Horie et al reported that prevalence of GIB was higher in AH patients who had died.(14) In this study by Horie et al, AH patients with and without GIB were compared using chi-square test.

Alcohol dose, ascites, encephalopathy, MDF and MELD were independently associated with mortality, using the multivariable Cox regression analysis in all AH patients with or without bleeding. This result is in accordance with the previous studies which report that MELD predicts mortality in AH patients.(6, 8, 9) According to Milan et al's study, MELD score predicts 30 day mortality in AH patients. Dunn et al reported that MELD was useful for predicting 30-day and 90-day mortality, but they did not provide data of period longer than 90 days. Our study elucidated factors predicting mortality with a longer observation time (maximum 5534 d) than the previous studies. Because ascites and encephalopathy are related to the decompensation of hepatic

function, it seems self-evident that such findings are associated with mortality. However, the drawback is that they are findings from physical examination performed by clinicians and thus, may lack objectivity. MDF also has a flaw because the prothrombin time calculated in seconds can vary according to the sensitivity of the thromboplastin reagent used.(3) Besides these parameters related to liver function, only alcohol dose was independently associated with mortality. This result is in accordance with the previous studies reporting that abstinence is the most important factor in predicting survival in AH patients.(16, 17) To improve survival of all the hospitalized AH patients, the abstinence from alcohol is thought to be important. A recent study by Potts et al indicated that mortality is increased significantly in AH patients who return to drinking.(18)

Using the multivariable Cox regression analysis in GIB group, we demonstrated that PHB and MELD score were independently associated with mortality. It is relatively well-known that MELD predicts mortality in AH patients.(6, 8, 9) On the other hand, portal hypertensive bleeding has never been evaluated as a predictor of mortality in AH patients. To the best of our knowledge, this is the first study to identify portal hypertensive bleeding as a risk factor of mortality in AH patients with GIB. We demonstrated that portal hypertensive bleeding is a parameter predicting poor survival outcome in AH patients experiencing GIB. When the endoscopic examination is performed in AH patients suspected to have GIB, clinicians should be scrupulous in describing the endoscopic findings. The endoscopist should carefully look for the origin of bleeding, and if there are multiple suspected sites of bleeding, the

most probable bleeding focus should be specified during the endoscopic examination. By prompt endoscopic examination of AH patients with GIB, physicians may stratify the risk of mortality in AH patients with GIB.

In a recent study using the large population-based National Inpatient Sample (NIS) dataset, the clinical characteristics and risk factors associated with in-patient mortality in hospitalized AH cases were reported.(5) However, in this study of Suthat et al, only in-patient mortality rate and factors associated with in-patient mortality were shown. There existed no mortality data after they were discharged from the hospitals. In addition, the NIS dataset is based on the International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes, and does not provide accurate clinical, laboratory and radiographic data. Their report could not specifically characterize AH patients on scoring system and mortality data were not identified after they were discharged from the hospitals. In our study, clinical scoring systems such as MDF and MELD were characterized, and survival data of patients who followed up for a long time were available. Survival data of the AH patients who were repetitively hospitalized and discharged were also available.

Since Imperiale et al reported that, after excluding subjects with GIB, corticosteroids (CS) reduced mortality in acute AH patients,(10) AH patients with GIB has been excluded from the indication of CS. Therefore, to date, no additional concrete data are available with regard to the use of CS in the treatment of AH patients with GIB. Our study, showing no significant difference of survival rate between Non-PHB group and Non-GIB group, may suggest that, as in Non-GIB patients, Non-PHB patients may also have benefit

from CS therapy. After appropriate pharmacologic or endoscopic treatment, AH patients with Non-PHB may be considered a candidate for treatment with CS.

Our study has some limitations. First, our study is a retrospective study and pathologic confirmation of AH was performed only in a small portion (34/329, 10.3%) of patients. However, all of the 34 patients in whom liver biopsy was performed showed results consistent with alcoholic hepatitis. The diagnosis of AH was mostly based on the clinical and laboratory parameters. Second, in our study, survival was verified with hospital record only. Social security death index was not investigated. Therefore, there are possibilities that the mortality rate in our data was lower than the actual rate.

In conclusion, GIB was associated with mortality in hospitalized AH patients. Among patients with GIB, PHB was associated with mortality, and the survival rate of Non-PHB group was not different from Non-GIB group. PHB is an independent predictor of mortality in hospitalized AH patients with GIB. Portal hypertensive bleeding and high MELD scores showed worse survival outcomes in AH patients with gastrointestinal bleeding. Therefore, the prompt endoscopic examination may help physicians to stratify the risk of mortality in AH patients with GIB.

Table 1. Comparison of clinical features between gastrointestinal bleeding (GIB) group and Non-GIB group

Variables	GIB group (N=132)	Non-GIB group (N=197)	*P* value
Male, n (%)	120 (90.9)	175 (88.8)	0.544
Age (yr)	50.6 ± 10.8	52.1 ± 10.1	0.210
Ascites	59 (44.7)	104 (52.8)	0.150
Hepatic encephalopathy	15 (11.4)	29 (14.7)	0.381
Alcohol dose (g/day)	132.4 ± 89.9	116.5 ± 74.7	0.082
Creatinine	1.0 ± 0.6	1.1 ± 1.2	0.648
Total bilirubin (mg/dL)	7.1 ± 7.2	7.4 ± 7.0	0.707
Prothrombin time (INR)	1.5 ± 0.5	1.5 ± 0.5	0.449
MDF	37.3 ± 27.8	35.4 ± 27.6	0.529
MELD	16.1 ± 7.4	16.0 ± 7.8	0.838

Table 2. Comparison of clinical features between portal hypertensive bleeding (PHB) group and Non-PHB group

Variables	PHB group (N=98)	Non-PHB group (N=34)	*P* value
Male, n (%)	90 (91.8)	30 (88.2)	0.505
Age (yr)	50.4 ± 10.5	51.1 ± 11.6	0.759
Ascites	55 (56.1)	9 (26.5)	0.003
Hepatic encephalopathy	20 (20.4)	3 (8.8)	0.125
RBC transfusion	2.9 ± 3.0	1.7 ± 2.3	0.034
Alcohol dose (g/day)	137.4 ± 96.0	118.1 ± 68.8	0.283
Creatinine	1.2 ± 0.8	1.1 ± 0.5	0.239
Total bilirubin (mg/dL)	7.7 ± 8.8	5.9 ± 5.5	0.283
Prothrombin time (INR)	1.7 ± 0.6	1.4 ± 0.4	0.005
MDF	46.8 ± 36.6	28.2 ± 22.8	0.006
MELD	18.8 ± 8.3	14.8 ± 7.4	0.016

Table 3. Causes of gastrointestinal bleeding in patients with alcoholic hepatitis

Cause	No. of patients	%	Hemostasis
Esophageal varix	76	57.6	EVL, SB tube, BB
Portal hypertensive gastropathy	19	14.4	BB, TIPS, supportive
Gastric ulcer	15	11.4	PPI, injection, clipping
Mallory-Weiss tear	12	9.1	clipping, band, injection
Duodenal ulcer	4	3.0	PPI, injection, clipping
Dieulafoy's lesion	3	2.3	band, clipping
Gastric varix	3	2.3	BRTO, EVO
Portal hypertensive colopathy	1	0.8	supportive

EVL, endoscopic variceal ligation; SB tube, Sengstaken-Blakemore tube; BB, beta blocker; TIPS, transjugular intrahepatic portosystemic shunt; PPI, proton pump inhibitor; BRTO, balloon-occluded retrograde transvenous obliteration; EVO, endoscopic variceal obturation

Table 4. Association between gastrointestinal bleeding (GIB) and mortality

	Death	Survival	Total	*P* value
GIB at 1st admission	N (%)	N (%)		
(+)	31 (41.3)	44 (58.7)	75	
(-)	89 (35.0)	165 (65.0)	254	
Total	120	209	329	0.320
GIB at any time	N (%)	N (%)		
(+)	64 (48.5)	68 (51.5)	132	
(-)	56 (28.4)	141 (71.6)	197	
Total	120	209	329	<0.001

Table 5. Univariable and multivariable analysis of risk factors for mortality in alcoholic hepatitis patients

Variables	Univariable		Multivariable	
	H.R. (95% C.I.)	*P* value	H.R. (95% C.I.)	*P* value
Male	0.968 (0.544-1.722)	0.911		
Female	*Ref.*			
Age	0.991 (0.974-1.009)	0.327		
Alcohol dose (g/day)	1.002 (1.000-1.004)	0.037	1.003 (1.001-1.005)	0.001
GIB at 1st admission	1.069 (0.706-1.619	0.751		
No GIB at 1st admission	*Ref.*			
Presence of ascites	1.844 (1.270-2.677)	0.001	2.067 (1.327-3.221)	0.001
Absence of ascites	*Ref.*			
Presence of encephalopathy	2.931 (1.936-4.436)	<0.001	3.232 (1.945-5.369)	<0.001
Absence of encephalopathy	*Ref.*			
Total bilirubin (mg/dL)	1.052 (1.028-1.075)	<0.001		
Creatinine	1.299 (1.180-1.431)	<0.001		
Prothrombin time (INR)	3.687 (2.715-5.007)	<0.001		
MDF	1.029 (1.022-1.035)	<0.001	1.014 (1.004-1.024)	0.006
MELD	1.102 (1.077-1.127)	<0.001	1.053 (1.016-1.091)	0.005

Table 6. Univariable and multivariable analysis of risk factors for mortality in alcoholic hepatitis patients with gastrointestinal bleeding

Variables	Univariable		Multivariable	
	H.R. (95% C.I.)	*P* value	H.R. (95% C.I.)	*P* value
Male	1.283 (0.514-3.203)	0.594		
Female	*Ref.*			
Age	0.981 (0.959-1.004)	0.103		
Portal hypertensive bleeding	3.141 (1.494-6.601)	0.003	2.178 (1.023-4.634)	0.043
Non-portal hypertensive bleeding	*Ref.*			
RBC transfusion	1.103 (1.013-1.202)	0.024		
Alcohol dose (g/day)	1.001 (0.999-1.004)	0.267		
Presence of ascites	3.368 (1.958-5.792)	<0.001		
Absence of ascites	*Ref.*			
Presence of encephalopathy	2.294 (1.290-4.080)	0.005		
Absence of encephalopathy	*Ref.*			
Total bilirubin (mg/dL)	1.052 (1.028-1.077)	<0.001		
Creatinine	1.893 (1.466-2.443)	<0.001		
Prothrombin time (INR)	3.156 (2.240-4.449)	<0.001		
MDF	1.020 (1.014-1.026)	<0.001		
MELD	1.102 (1.071-1.133)	<0.001	1.094 (1.063-1.127)	<0.001

Table 7. Causes of death in alcoholic hepatitis patients

Cause of death	No. of patients	%
Hepatic failure	26	21.7
Gastrointestinal bleeding	29	24.2
Hepatorenal syndrome	19	15.8
Infection	21	17.5
Cerebrovascular accident	5	4.2
Sudden arrest	15	12.5

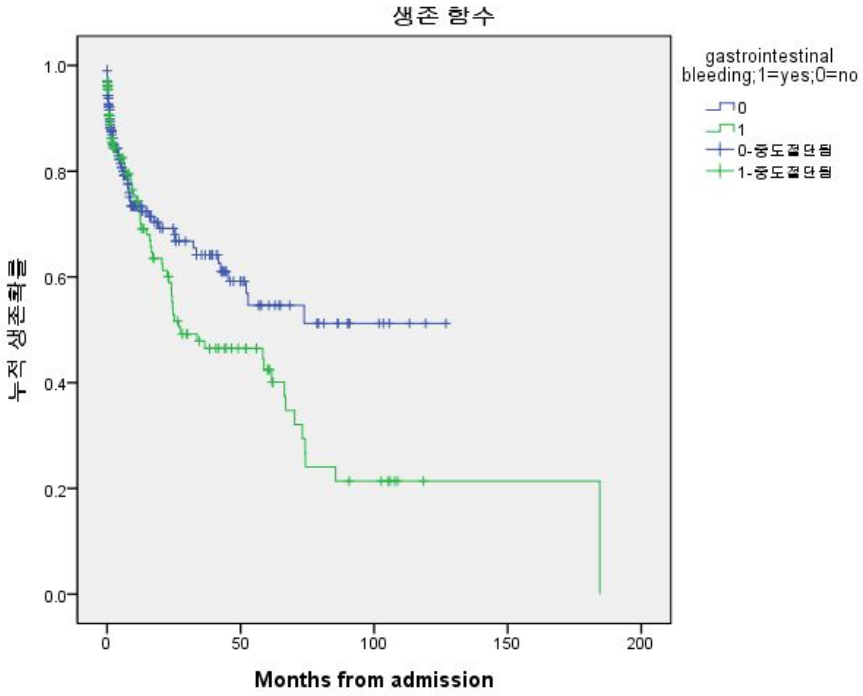

Fig 1. Comparison of survival between gastrointestinal bleeding (GIB) group and Non-GIB group (log rank test, P =0.034)

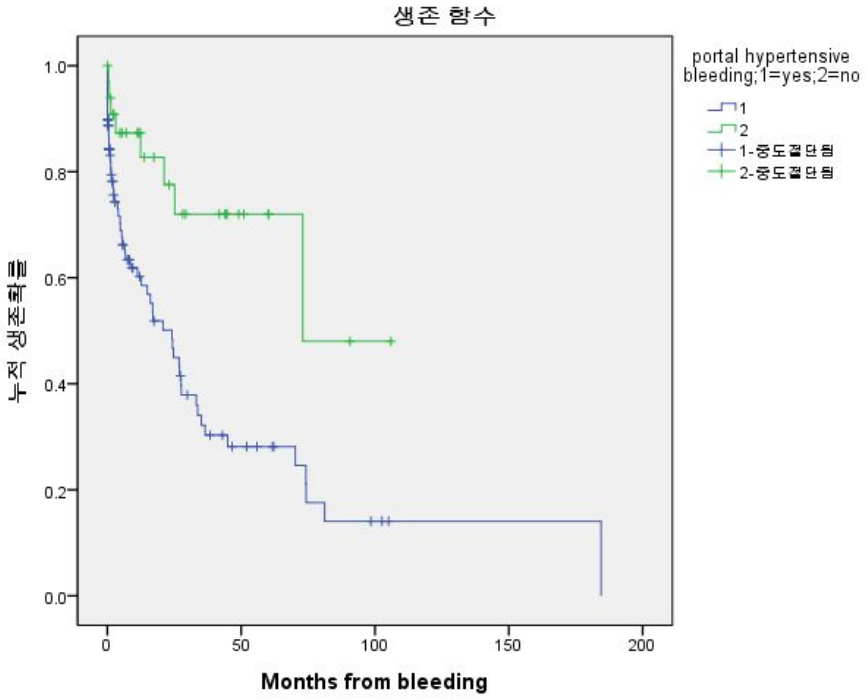

Fig 2. Comparison of survival between portal hypertensive bleeding (PHB) group and Non-PHB group (log rank test, *P*=0.001)

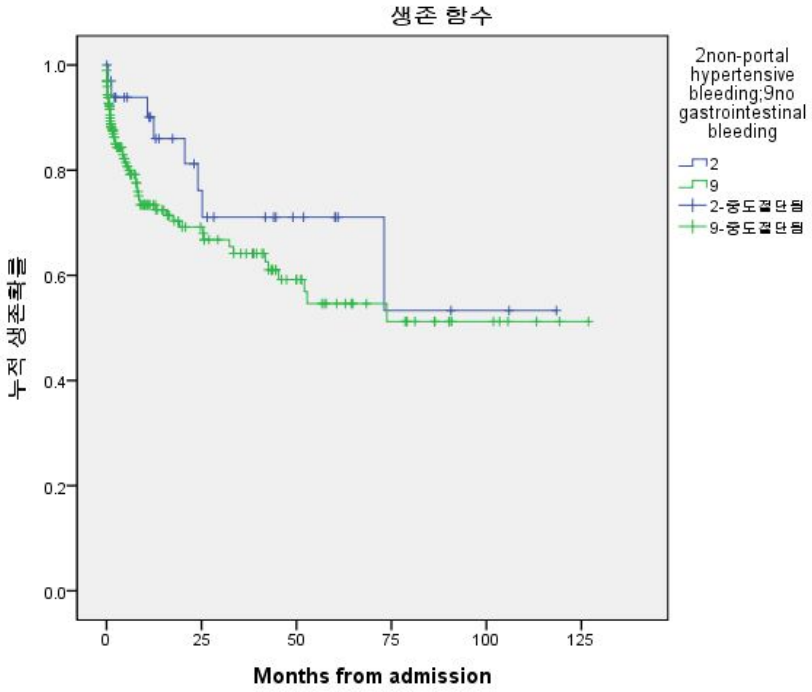

Fig 3. Comparison of survival between Non-PHB group and Non-GIB group (log rank test, *P*=0.213)

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국문 초록

서론: 위장관 출혈은 알코올성 간염 환자들에서 흔히 동반되는 증상이다. 본 연구에서는 알코올성 간염으로 입원한 환자들에서 발생한 위장관 출혈의 원인을 알아보았고, 위장관 출혈 유무가 알코올성 간염으로 입원한 환자들의 임상 양상과 생존에 미치는 영향에 대해 연구했으며, 생존 관련 요소들을 분석하였다.

방법: 1999년부터 2014년까지 알코올성 간염으로 입원한 환자들을 대상으로 후향적 코호트 연구를 수행하였다. 이들은 관찰 기간 중 위장관 출혈 경험 유무에 따라 두 군 (출혈군, 비출혈군)으로 나누어졌다. 출혈군은 첫 위장관 출혈시 출혈원인에 따라 문맥 고혈압 출혈군과 비문맥 고혈압 출혈군으로 나누어졌다. 위장관 출혈 유무와 문맥 고혈압 출혈 유무에 따라 알코올성 간염 환자들의 임상 양상과 생존 자료들이 분석되었다. 사망의 위험요소들을 파악하기 위해 콕스 회귀 분석법이 이용되었다.

결과: 알코올성 간염으로 입원했던 329명의 환자들이 연구에 포함되었다. 132명이 위장관 출혈을 경험하였고 출혈군에 포함되었다. 이들에서 위장관 출혈의 가장 흔한 원인은 식도정맥류 출혈이었다. 로그순위검정에서 출혈군은 비출혈군에 비해 사망률이 높았다. 문맥 고혈압 출혈군이 비문맥 고혈압 출혈군에 비해 사망률이 높았다. 비문맥 고혈압 출혈군과 비출혈군 간에는 유의한 사망률의 차이가 없었다. 알코올성 간염 환자 329명을 대상으로 한

다변량 분석에서 알코올 섭취량, 복수의 존재, 간성혼수, Maddrey's discriminant function (MDF), 그리고 model for end-stage liver disease (MELD) 점수가 사망과 관련됨이 확인되었다. 위장관 출혈을 동반한 알코올성 간염 환자 132명을 대상으로 한 다변량 분석에서는 MELD 점수와 문맥 고혈압 출혈이 사망과 독립적으로 관련되었음이 확인되었다.

결론: 높은 MELD 점수 외에 문맥 고혈압 출혈 여부가 위장관 출혈을 동반한 알코올성 간염 환자의 사망을 독립적으로 예측하였다. 따라서, 위장관 출혈을 동반한 알코올성 간염 환자에서 즉각적인 위내시경 검사를 통해 사망 위험성을 예측할 수 있을 것이다.

주요어: 알코올성 간염, 위장관 출혈, 문맥 고혈압, 생존

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