Original Article | http://dx.doi.org/10.3349/ymj.2012.53.2.318 pISSN: 0513-5796, eISSN: 1976-2437 | Yonsei Med J 53(2):318-327, 2012 | YMJ

Acute Variceal Hemorrhage in Patients with Liver Cirrhosis: Weekend versus Weekday Admissions

Sun Jeong Byun,[1*] Seung Up Kim,[1,2,3*] Jun Yong Park,[1,2,3] Beom Kyung Kim,[1] Do Young Kim,[1,2,3] Kwang Hyub Han,[1,2,3,4] Chae Yoon Chon,[1,2,3] and Sang Hoon Ahn[1,2,3,4]

[1]Department of Internal Medicine, [2]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul; [3]Liver Cirrhosis Clinical Research Center, Seoul; [4]Brain Korea 21 Project for Medical Science, Seoul, Korea.

Received: April 28, 2011
Revised: June 12, 2011
Accepted: June 20, 2011
Corresponding author: Dr. Sang Hoon Ahn, Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea.
Tel: 82-2-2228-1936, Fax: 82-2-393-6884
E-mail: ahnsh@yuhs.ac

*Sun Jeong Byun and Seung Up Kim contributed equally to this work.

· The authors have no financial conflicts of interest.

Purpose: Little is known about the impact of weekend admission on acute variceal hemorrhage (AVH). Thus, we investigated whether day of admission due to AVH influenced in-hospital mortality. **Materials and Methods:** We retrospectively reviewed the medical records of 294 patients with cirrhosis admitted between January 2005 and February 2009 for the management of AVH. Clinical characteristics were compared between patients with weekend and weekday admission, and independent risk factors for in-hospital mortality were determined by multivariate binary logistic regression analysis. **Results:** No demographic differences were observed between patients according to admission day or in the clinical course during hospitalization. Seventeen (23.0%) of 74 patients with weekend admission and 48 (21.8%) of 220 with weekday admission died during hospitalization (p=0.872). Univariate and subsequent multivariate analysis showed that initial presentation with hematochezia [p=0.042; hazard ratio (HR), 2.605; 95% confidence interval (CI), 1.038-6.541], in-patient status at the time of bleeding (p=0.003; HR, 4.084; 95% CI, 1.598-10.435), Child-Pugh score (p<0.001; HR, 1.877; 95% CI, 1.516-2.324), and number of endoscopy sessions for complete hemostasis (p=0.001; HR, 3.864; 95% CI, 1.802-8.288) were independent predictors for in-hospital mortality. **Conclusion:** Weekend admission did not influence in-hospital mortality in patients with cirrhosis who presented AVH.

Key Words: Cirrhosis, endoscopy, esophageal and gastric varices, hemorrhage, mortality

INTRODUCTION

Acute variceal hemorrhage (AVH), a frequent and often lethal complication of cirrhosis, occurs in up to 25% of patients with liver cirrhosis[1] and has a 6-week mortality rate of 15-20% with each episode.[2] Accordingly, AVH needs prompt endoscopic management. Previous studies have shown increased mortality for a number of medical and surgical conditions during weekend admissions,[3-10] which is known as the "weekend effect".[3] Postulating that delayed endoscopy due to less prepared facilities and staffing on weekends could cause a "weekend effect" for

outcome after upper gastrointestinal hemorrhage, Ananthakrishnan, et al.[11] recently attempted to prove this hypothesis in a large cohort study. However, in that study, the "weekend effect" was demonstrated only for non-variceal upper gastrointestinal hemorrhage, not for AVH. Although another study[12] focused on the "weekend effect" of AVH and reported no influences of weekend admission on the prognosis of AVH, data on the "weekend effect" of AVH to date have been limited. However, neither of these reports included key detailed patient characteristics such as the severity of liver function or endoscopic factors, which are powerful risk factors in AVH.[11,12] Because of these limitations, a chance remains that the effect of admission day and the optimal time between hospital arrival and endoscopy for better prognosis have not yet been clearly elucidated.

Thus, we investigated the impact of weekend admissions on in-hospital mortality using detailed demographic, clinical, laboratory, and endoscopic variables in patients with cirrhosis and AVH. We also evaluated whether time to endoscopy influenced in-hospital mortality in these patients.

MATERIALS AND METHODS

Data collection

We retrospectively reviewed the records of patients who were admitted to Severance Hospital (Yonsei University College of Medicine, Seoul, Korea) due to AVH between January 1, 2005 and February 28, 2009. To ensure consistency, one investigator performed the chart review, extracting demographic and admission data, initial vital signs and symptoms, endoscopic and laboratory variables, the degree of underlying hepatic reserve function, hospital charge, length of hospital stay, clinical course during hospitalization, in-hospital mortality, and causes of mortality.

Patients were followed through February 28, 2010. The median follow-up period was similar [8.6 months (range, 0.1-61.3) in patients with weekend admission vs. 8.4 months (range, 0.1-57.3) in those with weekday admission; log-rank test, p=0.698]. The study protocol confirmed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of our institution (IRB number, 4-2010-0391).

Patients

Total 521 admission cases with AVH were identified from the database using a principal or secondary diagnosis of esophageal variceal bleeding, according to diagnostic codes (I85.0, I98.2, and I86.4) of the 10th edition of the International Classification of Diseases. If a patient were admitted repeatedly during the study period, we selected only the first admission for the analysis to prevent statistical error, which excluded 165 cases of repeat admissions. We excluded patients with any missing data related to admission, discharge, endoscopy, laboratory findings, or in-hospital mortality (n=33). We also excluded patients who were initially identified as having AVH by first impression at the emergency room (ER) but who were ultimately confirmed as having non-variceal upper gastrointestinal hemorrhage or lower gastrointestinal bleeding by endoscopy (n=11). Patients with end stage liver failure who were expected to have extremely poor prognosis irrespective of AVH or endoscopic intervention (n=15), and those who received liver transplantations during hospitalization were also excluded (n=3). Ultimately, 294 patients were selected for the final analysis.

Hospital size, number of house staff, and on-call system for AVH

Our institute is a 2064-bed tertiary care teaching hospital that has been approved by the Joint Commission International since 2007. During the study period, the number of house staff responsible for the on-call system for AVH in the department of gastroenterology and hepatology consisted of 18 professors and 20 fellows. Our on-call system for AVH consists mainly of a stepwise notifying system from resident to fellows supervised by professors who provide 24-h coverage for all AVH cases.

Study variable definitions

An admission was defined as being on the weekend if the patient was admitted between midnight on Friday and midnight on Sunday. All others were categorized as weekday admissions. If bleeding occurred in an already hospitalized patient for another medical condition, which was included as in-patient status, weekend or weekday admissions were classified according to the time of symptom development. The time interval from subjective symptom development to admission (symptom to arrival time) was calculated in hours for patients who were admitted via the ER.

We divided patients by comorbidity at the time of admission as hepatocellular carcinoma (HCC) vs. other diseases, because HCC has been reported as a significant predictive

factor for death in decompensated cirrhosis and early rebleeding in several studies.[13,14] Comorbidities other than HCC included diabetes mellitus, essential hypertension, cardiovascular disease (history of angina, myocardial infarction, or congestive heart failure), respiratory disease (history of asthma, chronic obstructive lung disease, or current respiratory tuberculosis), renal failure (acute or chronic) including end-stage renal disease, and extrahepatic malignancies or infectious disease other than viral hepatitis. The overall degree of hepatic reserve function at the time of AVH was accessed using the Child-Pugh and Model for End-Stage Liver Disease (MELD) scores.[15]

Time to endoscopy was defined as the time interval from symptom development (for patients already in the hospital) or admission via the ER to initial endoscopy, expressed in hours. The form of gastroesophageal varices was evaluated according to the definition of the Japanese Research Society for Portal Hypertension.[16] Successful hemostasis at initial endoscopy was defined as the absence of identifiable bleeding at the end of endoscopy. The total number of endoscopy sessions for complete hemostasis was tabulated. If rebleeding occurred during hospitalization, the total number of endoscopy sessions during hospitalization was calculated. Rebleeding was defined as clinical evidence of active bleeding such as hematemesis or hematochezia observed after complete initial stabilization. Early rebleeding was defined within 5 days after initial variceal hemorrhage, according to the Baveno V criteria.[17]

On-call notification of patients with AVH

On-duty residents were notified of any patient with cirrhosis suspicious of upper gastrointestinal hemorrhage as indicated by one or more of the following symptoms: hematemesis, melena, hematochezia, or syncope and/or with blood in the nasogastric aspirate. Upon notification, the residents immediately evaluated each patient for initial hemodynamic status. Central catheterization and volume resuscitation using packed red blood cells and plasma expenders were conducted cautiously to prevent hypovolemic shock or ischemic change of vital organs if indicated. Once vital signs were stabilized, the chief resident notified the fellows and professors as to the feasibility of endoscopy. Finally, emergent endoscopy and its time were individualized at the discretion of the on duty professors considering patients age, hemodynamic status, and comorbidities.

Written informed content for endoscopy was obtained from the patients themselves or responsible family members before the procedure.

Treatment protocols for AVH

According to clinical practice guidelines, all patients with cirrhosis and AVH were managed by standard therapy. A combination of vasoconstrictor and endoscopic therapy [band ligation for esophageal variceal bleeding or histoacryl (B. Braun, Tuttlingen, Germany) injection therapy for gastric variceal bleeding],[18,19] together with short- term prophylactic antibiotics to prevent spontaneous bacterial peritonitis and other infections[20] were applied as soon as possible after the diagnosis of AVH.[17]

When immediate endoscopy was impossible at the time of admission due to uncontrolled massive bleeding or hemodynamic instability despite initial fluid and blood resuscitation, a Sengstaken-Blackmore tube was placed as a temporary 'bridge' therapy.[17] After the patient stabilized, endoscopy was attempted again, if indicated. If clinical symptoms and signs suggested pulmonary aspiration of bloody vomit or an altered mental status that precluded their ability to protect their airway, patients were admitted to an intensive care unit with endotracheal intubation. For these cases, an endoscopy session with portable equipment was attempted based on a clinical decision.[21]

A transjugular intrahepatic portosystemic shunt (TIPS) was placed for patients with intractable bleeding, frequent early rebleeding, or those who were unresponsive to endoscopic intervention.[17] After stabilization of the AVH, a β-blocker was administered as soon as possible, if no contraindications existed.

Statistical analyses

Statistical analyses were performed using SPSS (version 12.0, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the median (range) and were compared using an independent t-test. Categorical variables were expressed as percentages and were compared using the chi-square test. A two-tailed *p*-value of less than 0.05 was considered significant. Variables that were statistically significant in the univariate analysis were subsequently included in a multivariate stepwise logistic regression model to identify independent predictors for in-hospital mortality. Rebleeding was compared using the log rank test with a Kaplan-Meier analysis. Receiver operating characteristics (ROC) curves and the area under ROC curves (AUROC) were used to estimate the respective optimal cutoff time.

RESULTS

Patient characteristics

For all study population, the median age was 54 years (range, 27-83) and male gender predominated (n=239, 81.3%). Sixty-two (21.1%) patients were in-patients status at the time of bleeding and the other 232 (78.9%) were admitted via the ER. Eighty-five (28.9%) patients had a previous history of AVH. The most common etiology of liver cirrhosis was hepatitis B virus infection (n=136, 46.3%). One-hundred twenty-nine patients (43.9%) had HCC at the time of admission. The median Child-Pugh score was 8 (range, 5-15), and the median MELD [15] score was 13 (range, 5-42).

Table 1. Baseline Characteristics of Patients with Weekend and Weekday Admission due to Acute Variceal Hemorrhage

	Weekend (n=74, 25.2%)	Weekday (n=220, 74.8%)	*p* value
Age (yrs)	55 (31-83)	56 (27-83)	0.758
Male gender	60 (81.1)	179 (81.4)	0.999
Patient status at the time of bleeding			0.586
In-patient status	15 (20.3)	47 (21.4)	
In liver dept./In other dept.	12/3	41/6	
Admission via emergency room	59 (79.7)	173 (78.6)	
From other clinic/from home	8/51	15/158	
Symptom to arrival time (h)	7.0 (0.5-239.7)	8.6 (0.2-318.1)	0.529
Initial hemodynamic parameters			
Heart rate (beats/min)	94 (55-150)	91 (52-160)	0.323
Mean blood pressure (mm Hg)	82 (43.3-117.3)	78 (13.3-159.7)	0.580
Systolic blood pressure (mm Hg)	110 (50-164)	106 (40-166)	0.314
Diastolic blood pressure (mm Hg)	68 (38-95)	63 (30-161)	0.388
Initial presenting symptom			0.837
Melena/hematemesis/hematochezia/ others*	11 (14.9)/49 (66.2)/ 12 (16.2)/2 (2.7)	38 (17.3)/134 (60.9)/ 43 (19.5)/5 (2.3)	
Amount of bleeding (cc)	360 (10-3000)	300 (10-3000)	0.701
Previous history of AVH	18 (24.3)	67 (30.5)	0.374
Etiology of cirrhosis			0.623
B-viral/C-viral/alcoholic/others	34 (45.9)/9 (12.2)/ 22 (29.7)/9 (12.3)	102 (46.4)/28 (12.7)/ 52 (23.6)/38 (17.3)	
Comorbities at admission			0.380
Coexisting hepatocellular carcinoma	37 (50.0)	92 (41.8)	
Other than hepatocellular carcinoma†	17 (23.0)	51 (23.2)	
Laboratory tests			
Serum hemoglobin (mg/dL)	8.9 (3.2-17.1)	8.8 (3.0-13.9)	0.694
Serum albumin (mg/dL)	2.7 (1.3-4.0)	2.9 (1.6-4.2)	0.084
Total bilirubin (mg/dL)	1.6 (0.3-38.8)	1.6 (0.3-28.5)	0.565
Prothrombin time (INR)	1.37 (1.07-2.99)	1.31 (0.9-4.07)	0.228
Platelet count (10^3/mm^3)	97.5 (14-537)	104 (11-380)	0.259
Alanine aminotransferase (IU/L)	41.5 (9-907)	31 (7-688)	0.192
Blood urea nitrogen (mg/dL)	29.1 (7.5-102.7)	24 (8.3-108.1)	0.599
Creatinine (mg/dL)	0.96 (0.59-13.2)	0.9 (0.4-9.7)	0.359
Ammonia (μg/dL)	63 (22-249)	69 (24-253)	0.380
Child-Pugh score	8 (6-13)	8 (5-15)	0.485
MELD score	14 (5-42)	13 (5-41)	0.647

AVH, acute variceal hemorrhage; Dept., department; INR, international normalized ratio; MELD, The Model for End-Stage Liver Disease; HCC, hepatocelluar carcinoma.

Variables are expressed as median (range), n (%), or n.

*Others symptoms includes syncope and dizziness.

†Comorbidity other than hepatocellular carcinoma includes diabetes mellitus, essential hypertension, cardiovascular disease, respiratory disease or dyspnea at rest, acute or chronic renal failure, malignancy other than HCC, previous organ transplantation, or infection.

The baseline characteristics of patients with weekend and weekday admissions due to AVH are compared in Table 1. Seventy-four (25.2%) patients were admitted on a weekend compared to 220 (74.8%) on a weekday. Serum albumin level trended toward a difference between groups with borderline significance (p=0.084), but otherwise no significant differences were observed between patients with weekend admissions and those with weekday admissions among the demographic, clinical, and laboratory elements evaluated.

Endoscopic findings, interventions, and outcomes

No statistical differences were observed on the endoscopic findings or interventions based on the day of admission (Table 2). The median time interval from admission via the ER or symptom development to initial endoscopy (time to endoscopy) was 11.3 h in patients with weekend admission and 7.5 h in those with weekday admission (p=0.178). Initial endoscopic findings indicated that high-grade esophageal varices (F2, 44.9% and F3, 36.4%) were frequently associated with AVH in all patients. Endoscopic intervention and the success rate of the initial endoscopy were not significantly different between the two groups (p=0.999 and p=0.671, respectively). Twelve (16.2%) patients with weekend admission and 46 (21.0%) with weekday admission received more than two sessions of endoscopy due to recurrent bleeding during hospitalization. Two (2.7%) patients with weekend admission and five (2.3%) with weekday admission received TIPS during hospitalization (p=0.999).

Clinical course and outcomes during hospitalization

Table 3 summarizes the clinical course and outcome during hospitalization for patients with weekend and weekday admissions. Hepatic encephalopathy, ascitic decompensation, and hyperbilirubinemia were the most common complications related to liver cirrhosis regardless of the day of admission, and no significant differences were observed in the development of complications during hospitalization (all p>0.05). Admission to the intensive care unit, length of hospital stay, and hospital charges also were not different between the two groups (all p>0.05). Seventeen (23.0%) patients with weekend admission and 48 (21.8%) with weekday admission died during hospitalization (p=0.872).

Rebleeding

During the study period, 130 of 294 (44.2%) patients experienced rebleeding, among which 21 (7.1%) showed early rebleeding (within 5 days). The early rebleeding rate after complete hemostasis and median time interval from complete hemostasis to early rebleeding were not different between patients with weekend and weekday admission [5.4% (n=4) vs. 7.7% (n=17); p=0.502 and median 67.9 h (range 7.9-97.1) vs. 56.2 h (range 7.7-109.2); log rank test, p=0.422].

Table 2. Endoscopic Findings, Interventions and Outcomes

	Weekend (n=74)	Weekday (n=220)	p value
Time to endoscopy (h)*	11.3 (1.0-355.7)	7.5 (0.1-305.3)	0.178
Esophageal varix			0.124
F0/F1/F2/F3	6 (8.1)/13 (17.6)/33 (44.6)/ 22 (29.7)	6 (2.7)/30 (13.6)/98 (44.6)/ 86 (39.1)	
Cardiac varix			0.312
Nonvisible or F0/F1/F2/F3	31 (41.9)/20 (27.0)/14 (18.9)/ 9 (12.2)	93 (42.3)/58 (26.4)/56 (25.5)/ 13 (5.8)	
Stigmata of recent hemorrhage EV/ CV/ nonvisible	38 (51.3)/21 (28.4)/15 (20.3)	124 (56.4)/50 (22.7)/46 (20.9)	0.296
Intervention			0.999
Endoscopy only/with EVL and/or Histoacryl	13 (17.6)/61 (82.4)	38 (17.4)/182 (83.6)	
Successful hemostasis at first endoscopy	65 (87.8)	196 (89.5)	0.671
Number of endoscopy sessions for complete hemostasis	1 (1-6)	1 (1-4)	0.333
One/two/more than three	62 (83.8)/9 (12.2)/3 (4.0)	174 (79.0)/40 (18.3)/6 (2.7)	
TIPS during hospitalization	2 (2.7)	5 (2.3)	0.999

CV, cardiac varix; EV, esophageal varix; EVL, esophageal variceal ligation; TIPS, transjugular intrahepatic portosystemic shunt.
Variables are expressed as median (range) or n (%).
*Time to endoscopy indicates time interval from admission via emergency room or symptom development (for patients with in-patient state) to initial endoscopy.

Table 3. Clinical Course and Outcomes during Hospitalization

	Weekend (n=74)	Weekday (n=220)	*p* value
Complications during hospitalization			
Hepatic encephalopathy	19 (25.7)	59 (26.8)	0.880
Ascitic decompensation	19 (25.7)	62 (28.2)	0.764
Hyperbilirubinemia	24 (32.4)	73 (33.2)	0.999
Renal failure	11 (14.9)	40 (18.2)	0.598
Hepatorenal syndrome	3 (4.1)	24 (10.9)	0.056
Respiratory failure requiring mechanical ventilation	9 (12.2)	13 (5.9)	0.121
Spontaneous bacterial peritonitis	3 (4.1)	13 (5.9)	0.454
Hypovolemic shock requiring inotropics	13 (17.6)	35 (15.9)	0.719
Infection other than spontaneous bacterial peritonitis	8 (10.8)	32 (14.5)	0.310
Admission to intensive care unit	10 (13.5)	20 (9.1)	0.274
Length of hospital stay	9.2 (1.7-68.6)	9.9 (0.53-97.0)	0.165
Hospital charge ($)	5066 (1103-33602)	4853 (1151-48302)	0.402
In-hospital mortality	17 (23.0)	48 (21.8)	0.872

Variables are expressed as median (range) or n (%).

Table 4. Causes of In-Hospital Mortality

	Weekend (n=17)	Weekday (n=48)	*p* value
Variceal bleeding	8 (47.0)	20 (41.7)	
Hepatic failure	5 (29.4)	14 (29.2)	
Hepatocellular carcinoma*	1 (5.9)	4 (8.3)	0.965
Hepatorenal syndrome	2 (11.8)	4 (8.3)	
Infection	1 (5.9)	6 (12.5)	

HCC, hepatocelluar carcinoma.
Variables are expressed as n (%).
Death caused from hepatocellular carcinoma* included hemoperitoneum due to HCC rupture or progression of HCC.

Causes of in-hospital mortality

The most common causes of death were variceal bleeding in 28 (43.1%) patients and hepatic failure in 19 (29.2%), irrespective of weekend or weekday admission (Table 4). Five (1.7%) patients died of hemoperitoneum due to HCC rupture or progression of HCC. The other 13 patients died of hepatorenal syndrome and infection including aspiration pneumonia. No significant differences were observed for the causes of in-hospital mortality between patients with weekend and those with weekday admission (p=0.965).

Predictors of in-hospital mortality of AVH

Overall, 65 (22.1%) patients died during the study period. Univariate and subsequent multivariate binary logistic regression analyses to identify the independent risk factors are shown in Table 5. Age, male gender, initial hemodynamic parameters, amount of bleeding, previous history of AVH, etiology of cirrhosis, coexisting HCC, hemoglobin, serum albumin and creatinine, time to endoscopy, presence of stigmata, grade of varices, successful hemostasis at first endoscopy and TIPS during hospitalization did not significantly predict in-hospital mortality (all p>0.05). After adjusting for other factors that were significant in the univariate analyses, the in-hospital mortality of AVH was remarkably dependent on initial presentation with hematochezia [p=0.042; hazard ratio (HR)=2.605; 95% confidence interval (CI), 1.038-6.541], in-patient status at the time of bleeding (p=0.003; HR=4.084; 95% CI, 1.598-10.435), Child-Pugh score (p<0.001; HR=1.877; 95% CI, 1.516-2.324), and number of endoscopy sessions for complete hemostasis (p=0.001; HR=3.864; 95% CI, 1.802-8.288).

The correlation between time to endoscopy and in-hospital mortality

Although no significant correlation was observed between the time to endoscopy and in-hospital mortality for the overall study population, we further analyzed the timing of endoscopy after risk stratification of the study patients. For grouping patients, we used the following pre-endoscopic independent predictors described in Table 5: initial presentation with hematochezia, in-patient status at the time of bleeding and Child-Pugh score. Then, we checked whether

Table 5. Univariate and Subsequent Multivariate Analysis to Identify Independent Predictors of In-Hospital Mortality

	Univariate	Multivariate		
	p value	*p* value	HR	95% CI
Initial presentation of acute variceal hemorrhage				
Hematochezia vs. other symptoms*	0.001	0.042	2.605	1.038-6.541
Patient status at the time of variceal bleeding				
In-patient vs. admission via emergency room	0.001	0.003	4.084	1.598-10.435
Platelet count (10^3/mm^3)	0.027	0.787		
Total bilirubin (mg/dL)	<0.001	0.570	-	-
Prothrombin time (INR)	0.003	0.332		
Alanine aminotransferase (IU/L)	0.001	0.070	-	-
Blood urea nitrogen (mg/dL)	0.006	0.568		
Child-Pugh score	<0.001	<0.001	1.877	1.516-2.324
Time to endoscopy (h)†	0.025	0.325		
Number of endoscopy sessions for complete hemostasis	<0.001	0.001	3.864	1.802-8.288
Successful hemostasis at first endoscopy	0.001	0.975		
Length of hospital stay (day)	<0.001	0.998	-	-
Weekend vs. weekday	0.892	0.563	-	-

CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; ER, energency room.
Reference values: other symptoms*, admission via emergency room, and weekday.
*Other symptoms include melena, hematemesis, syncope and dizziness.
†Time to endoscopy indicate time interval from admission via ER or symptom development (for already hospitalized patients) to initial endoscopy.

time to endoscopy independently influenced in-hospital mortality in each subgroup by multivariate binary logistic analyses. Finally, if time to endoscopy showed a statistical significance, we used the ROC curve to estimate the optimal cutoff time point.

As a result, the influence of time to endoscopy on in-hospital mortality was identified as significant in a subgroup of patients with hematochezia (p=0.001; HR=6.81; 95% CI, 1.582-29.311) and those with Child-Pugh B and C (p=0.026; HR=3.386; 95% CI, 1.110-9.475). The corresponding ROC curve analysis showed 12.5 h as the optimal cutoff time to endoscopy (sensitivity, 61.9%; specificity, 77.4%) in patients with hematochezia (AUROC, 0.676; p=0.037; 95% CI, 0.516-0.836) and 16.7 h (sensitivity, 60.6%; specificity, 66.0%) in those with Child-Pugh B or C (AUROC, 0.625; p=0.033; 95% CI, 0.505-0.744).

DISCUSSION

This study investigated independent predictors of in-hospital mortality in patients with cirrhosis who presented with AVH and the optimal time to endoscopy in subgroups of the study population. We did not identify a negative impact of weekend admission on mortality in patients with AVH, but we were able to identify an optimal time to endoscopy in several subgroups of patients.

Faced with economic problems and market realities, hospitals have reduced the number of available staff and facilities for diagnostic and therapeutic procedures during weekends. In their analysis of 126754 emergently hospitalized patients, Bell and Redelmeier[22] in Canada demonstrated relatively longer wait times for six urgent procedures during weekend admission including endoscopy (all p<0.001). Furthermore, staff on weekends might be less experienced and less specialized than those working on weekdays. These differences can be justified if no significant difference exists in treatment outcomes according to the timing of admissions, but hospitals must maintain staffing and facilities at weekday levels of availability if patient outcome is clearly affected. Although patients hospitalized on weekends seemed to have longer median wait time for endoscopy in our study (11.3 h in weekend admission vs. 7.5 h in weekday admission, p=0.178), it was not long enough to cause a weekend effect in our study.

In another landmark study, Bell and Redelmeier[3] in Canada reported significantly higher mortality for several acute diagnoses including acute epiglottitis, ruptured abdominal aortic aneurysm, and pulmonary embolism for patients who were hospitalized on weekends. Similarly, Cram, et al.[4] found higher mortality following weekend admission. The negative correlation of weekend admission with poor outcome has been observed among diverse patient groups, including those requiring admission to an intensive care unit[5,6]

and those experiencing stroke,[7] hip fracture,[8] appendicitis,[9] myocardial infarction,[8,10,23] and peptic ulcer disease[24] in specific hospital settings.

Myers, et al.[12] first reported that weekend admission in patients with esophageal variceal hemorrhage was associated only with a small delay in endoscopy and no increase in mortality. Although time to endoscopy and the events of hepatic decompensation were adjusted in that study,[12] Child-Pugh class or MELD score, endoscopic variables, and initial hemodynamic status, all of which have been reported as important prognostic predictors,[1,13,25,26] were not incorporated into the analysis. Additionally, the study may have selected for patients with relatively less severe disease by only enrolling those who were admitted via the ER and excluding those who experienced AVH when already hospitalized from other diseases. Accordingly, the results of Myers, et al.[12] should be interpreted cautiously, and we specifically attempted to determine the effects of these factors on in-hospital mortality in the present study.

To date, several risk factors for mortality due to AVH have been identified, including liver function as estimated by Child-Pugh or MELD score,[25,26] and the presence of HCC,[13] portal hypertension,[13] and circulatory dysfunction.[13] In our study, initial presentation with hematochezia, in-patient status at the time of bleeding, Child-Pugh score, and the number of endoscopy sessions for complete hemostasis were selected as independent prognostic factors of in-hospital mortality. Considering the significant correlation between initial presentation with hematochezia and systolic blood pressure <100 mm Hg (p=0.043), pulse rate >100/min (p=0.019), and the use of inotropics (p=0.002), hematochezia at the time of bleeding seemed to reflect an unstable hemodynamic status due to more active bleeding, which ultimately caused more in-hospital mortality. The influence of unstable hemodynamics on in-hospital mortality due to AVH is further supported by Bambha, et al.,[26] who recently reported that a MELD score ≥18, active bleeding at endoscopy, or transfusion of ≥4 units of packed red blood cells within 24 h were each independent predictors of in-hospital mortality. A secondary insult due to variceal bleeding in a patient already hospitalized for a separate medical condition could result in poorer outcome, which may explain why in-patient status was another independent predictor of in-hospital mortality in our study. Child-Pugh score, a traditional risk factor for patients with liver cirrhosis, was also predictive, as expected.[17] Our finding that the number of endoscopy sessions for complete hemostasis was an independent predictor of in-hospital mortality was in agreement with a previous study by Hsu, et al.[27]

A new concept of serum ammonia level as a marker of the presence of varix due to portal hypertension which can influence the prognosis of patients with cirrhosis was proposed,[28] however, it was not selected as an independent predictor of in-hospital mortality in our study. However, considering the retrospective design of our study, the predictive role of serum ammonia level which is correlated to the presence of varix with portal hypertension should be investigated in the future prospective study.

Previous meta-analyses have revealed that pharmacotherapy with vasoactive drugs such as terlipressin or somatostatin combined with endoscopic sclerotherapy or band-ligation can reduce the rate of rebleeding and all causes of mortality,[29-31] making these methods standard therapy.[2,29] However, controversy still surrounds the optimal time to endoscopy.[27,32] Current guidelines from major professional societies recommend that endoscopic intervention be performed within 12 h of admission in patients with cirrhosis without solid evidences.[17,33] Although the time to endoscopy was not associated with in-hospital mortality for all patients in our study, it was significant in subgroups of patients presenting with hematochezia or poor liver function of Child-Pugh class B or C (optimal cutoff time to endoscopy of 12.5 and 16.7 h, respectively) and very similar to current guidelines. Recently, Garcia-Tsao and Bosch[2] proposed different treatment strategies for AVH according to risk stratification, recommending pharmacologic therapy alone for patients at low risk (Child-Pugh class A) and more aggressive management in patients at moderate to high risk (Child-Pugh class B or C or hepatic venous pressure gradient >20 mm Hg), which is in support with our results.

Our study has several strengths. First, we tried to minimize selection bias by investigating a wide range of patients with AVH, including those with unstable hemodynamics and in-patient status at the time of bleeding who were excluded in previous studies.[11,12] Second, we demonstrated the potential significance of time to endoscopy in subgroups of patients with AVH who presented with hematochezia and poor liver function. However, we are also aware of several limitations of our study. First, because a comparative analysis between our institution and a primary or secondary medical center was not available, our results should be interpreted with caution and cannot be applied to primary or secondary medical centers. Second, we did not consider public holidays that fell on a weekday, which could resemble a weekend day in hos-

pital staffing and available facilities.

In conclusion, weekend admission and time to endoscopy did not influence in-hospital mortality in patients with cirrhosis who presented with AVH. Initial presentation with hematochezia, in-patient status at the time of bleeding, Child-Pugh score, and number of endoscopy sessions for complete hemostasis were strongly associated with in-hospital mortality. Because early endoscopy might be life-saving in patients who present with hematochezia or Child-Pugh class B or C, well designed prospective trials are needed to identify high risk patients and design effective, tailored management strategies.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Korea Healthcare technology R & D project, Ministry of Health and Welfare, Republic of Korea (A102065), and in part by a grant from the Brain Korea 21 Project for Medical Science.

REFERENCES

1. North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988;319:983-9.
2. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med 2010;362:823-32.
3. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. N Engl J Med 2001;345:663-8.
4. Cram P, Hillis SL, Barnett M, Rosenthal GE. Effects of weekend admission and hospital teaching status on in-hospital mortality. Am J Med 2004;117:151-7.
5. Ensminger SA, Morales IJ, Peters SG, Keegan MT, Finkielman JD, Lymp JF, et al. The hospital mortality of patients admitted to the ICU on weekends. Chest 2004;126:1292-8.
6. Hixson ED, Davis S, Morris S, Harrison AM. Do weekends or evenings matter in a pediatric intensive care unit? Pediatr Crit Care Med 2005;6:523-30.
7. Saposnik G, Baibergenova A, Bayer N, Hachinski V. Weekends: a dangerous time for having a stroke? Stroke 2007;38:1211-5.
8. Clarke MS, Wills RA, Bowman RV, Zimmerman PV, Fong KM, Coory MD, et al. Exploratory study of the 'weekend effect' for acute medical admissions to public hospitals in Queensland, Australia. Intern Med J 2010;40:777-83.
9. Doria AS, Amernic H, Dick P, Babyn P, Chait P, Langer J, et al. Cost-effectiveness analysis of weekday and weeknight or weekend shifts for assessment of appendicitis. Pediatr Radiol 2005;35:1186-95.
10. Kostis WJ, Demissie K, Marcella SW, Shao YH, Wilson AC, Moreyra AE; Myocardial Infarction Data Acquisition System (MIDAS 10) Study Group. Weekend versus weekday admission and mortality from myocardial infarction. N Engl J Med 2007;356:1099-109.
11. Ananthakrishnan AN, McGinley EL, Saeian K. Outcomes of weekend admissions for upper gastrointestinal hemorrhage: a nationwide analysis. Clin Gastroenterol Hepatol 2009;7:296-302e1.
12. Myers RP, Kaplan GG, Shaheen AM. The effect of weekend versus weekday admission on outcomes of esophageal variceal hemorrhage. Can J Gastroenterol 2009;23:495-501.
13. Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding--unresolved issues. Summary of an American Association for the study of liver diseases and European Association for the study of the liver single-topic conference. Hepatology 2008;47:1764-72.
14. Toubia N, Sanyal AJ. Portal hypertension and variceal hemorrhage. Med Clin North Am 2008;92:551-74.
15. Boursier J, Cesbron E, Tropet AL, Pilette C. Comparison and improvement of MELD and Child-Pugh score accuracies for the prediction of 6-month mortality in cirrhotic patients. J Clin Gastroenterol 2009;43:580-5.
16. Idezuki Y. General rules for recording endoscopic findings of esophagogastric varices (1991). Japanese Society for Portal Hypertension. World J Surg 1995;19:420-2.
17. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2005;43:167-76.
18. Baik SK, Jeong PH, Ji SW, Yoo BS, Kim HS, Lee DK, et al. Acute hemodynamic effects of octreotide and terlipressin in patients with cirrhosis: a randomized comparison. Am J Gastroenterol 2005;100:631-5.
19. Chung JB, Nam DK, Han KH, Kim WH, Kim DY, Chon CY, et al. Endoscopic injection sclerotherapy in patients with bleeding esophageal varices: a retrospective analysis. Korean J Intern Med 1990;5:5-14.
20. Cho BC, Lee JH, Park JW, Hong CS, Kim JM, Kang SM, et al. Subacute bacterial endocarditis associated with upper endoscopy. Yonsei Med J 2004;45:936-40.
21. Bendtsen F, Krag A, Møller S. Treatment of acute variceal bleeding. Dig Liver Dis 2008;40:328-36.
22. Bell CM, Redelmeier DA. Waiting for urgent procedures on the weekend among emergently hospitalized patients. Am J Med 2004;117:175-81.
23. Redelmeier DA, Bell CM. Weekend worriers. N Engl J Med 2007;356:1164-5.
24. Shaheen AA, Kaplan GG, Myers RP. Weekend versus weekday admission and mortality from gastrointestinal hemorrhage caused by peptic ulcer disease. Clin Gastroenterol Hepatol 2009;7:303-10.
25. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481-8.
26. Bambha K, Kim WR, Pedersen R, Bida JP, Kremers WK, Kamath PS. Predictors of early re-bleeding and mortality after acute variceal haemorrhage in patients with cirrhosis. Gut 2008;57:814-20.
27. Hsu YC, Chung CS, Tseng CH, Lin TL, Liou JM, Wu MS, et al. Delayed endoscopy as a risk factor for in-hospital mortality in cirrhotic patients with acute variceal hemorrhage. J Gastroenterol Hepatol 2009;24:1294-9.
28. Tarantino G, Citro V, Esposito P, Giaquinto S, de Leone A, Milan

G, et al. Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. BMC Gastroenterol 2009;9:21.
29. Bañares R, Albillos A, Rincón D, Alonso S, González M, Ruiz-del-Arbol L, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. Hepatology 2002;35:609-15.
30. Ravipati M, Katragadda S, Swaminathan PD, Molnar J, Zarling E. Pharmacotherapy plus endoscopic intervention is more effective than pharmacotherapy or endoscopy alone in the secondary prevention of esophageal variceal bleeding: a meta-analysis of randomized, controlled trials. Gastrointest Endosc 2009;70:658-64.e5.
31. D'Amico G, Pietrosi G, Tarantino I, Pagliaro L. Emergency sclerotherapy versus vasoactive drugs for variceal bleeding in cirrhosis: a Cochrane meta-analysis. Gastroenterology 2003;124:1277-91.
32. Cheung J, Soo I, Bastiampillai R, Zhu Q, Ma M. Urgent vs. non-urgent endoscopy in stable acute variceal bleeding. Am J Gastroenterol 2009;104:1125-9.
33. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey WD; Practice Guidelines Committee of American Association for Study of Liver Diseases; Practice Parameters Committee of American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Am J Gastroenterol 2007;102:2086-102.