J Korean Med Sci. 2018 Mar 19;33(12):e99
https://doi.org/10.3346/jkms.2018.33.e99
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article

Gastroenterology & Hepatology

Check for updates

Follow-up Creatinine Level Is an Important Predictive Factor of In-hospital Mortality in Cirrhotic Patients with Spontaneous Bacterial Peritonitis

Baek Gyu Jun [1*] **Woong Cheul Lee** [2*] **Jae Young Jang** [2] **Soung Won Jeong** [2] **Young Don Kim** [1] **Gab Jin Cheon** [1] **Yun Nah Lee** [3] **Sang Gyune Kim** [3] **Young Seok Kim** [3] **Young Sin Cho** [4] **Sae Hwan Lee** [4] **and Hong Soo Kim** [4]

[1]Department of Internal Medicine, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung, Korea
[2]Institute for Digestive Research and Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea
[3]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Korea
[4]Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, Korea

Received: Sep 29, 2017
Accepted: Jan 5, 2018

Address for Correspondence:
Jae Young Jang, MD, PhD
Institute for Digestive Research and Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Soonchunhyang University Hospital, 59 Daesagwan-ro, Yongsan-gu, Seoul 04401, Korea.
E-mail: jyjang@schmc.ac.kr

*Baek Gyu Jun and Woong Cheul Lee contributed equally to this work.

ORCID iDs
Baek Gyu Jun
https://orcid.org/0000-0003-4693-9542
Woong Cheul Lee
https://orcid.org/0000-0002-6745-7334
Jae Young Jang
https://orcid.org/0000-0001-5335-752X
Soung Won Jeong
https://orcid.org/0000-0003-2855-6011
Young Don Kim
https://orcid.org/0000-0001-9003-9862

ABSTRACT

Background: Spontaneous bacterial peritonitis (SBP) is one of the severe complications of liver cirrhosis. Early detection of high-risk patients is essential for prognostic improvement. The aim of this study is to investigate the predictive factors related to in-hospital mortality in patients with SBP.
Methods: This was a retrospective study of 233 SBP patients (181 males, 52 females) who were admitted to four tertiary referral hospitals between August 2002 and February 2013. The patients' laboratory and radiologic data were obtained from medical records. The Child-Turcotte-Pugh (CTP) score and model for end-stage liver disease sodium model (MELD-Na) scores were calculated using the laboratory data recorded at the time of the SBP episode.
Results: The causes of liver cirrhosis were hepatitis B (44.6%), alcohol (43.8%), hepatitis C (6.0%), and cryptogenic cirrhosis (5.6%). The mean MELD-Na and CTP scores were 27.1 and 10.7, respectively. Thirty-one of the patients (13.3%) died from SBP in hospital. Multivariate analysis revealed that maximum creatinine level during treatment was a statistically significant factor for in-hospital mortality ($P = 0.005$). The prognostic accuracy of the maximum creatinine level during treatment was 78.0% ($P < 0.001$). The optimal cutoff point for the maximum serum creatinine was 2 mg/dL ($P < 0.001$).
Conclusion: The follow-up creatinine level during treatment is an important predictive factor of in-hospital mortality in cirrhotic patients with SBP. Patients with SBP and a serum creatinine level during treatment of ≥ 2.0 mg/dL might have a high risk of in-hospital mortality.

Keywords: Liver Cirrhosis; Spontaneous Bacterial Peritonitis; Renal Function; Serum Creatinine Level

Gab Jin Cheon
https://orcid.org/0000-0001-5937-5999
Yun Nah Lee
https://orcid.org/0000-0001-5588-784X
Sang Gyune Kim
https://orcid.org/0000-0001-8694-777X
Young Seok Kim
https://orcid.org/0000-0002-7113-3623
Young Sin Cho
https://orcid.org/0000-0001-7090-2921
Sae Hwan Lee
https://orcid.org/0000-0001-8320-5914
Hong Soo Kim
https://orcid.org/0000-0003-3966-9302

Funding

This work was supported by the Soonchunhyang University Research Fund (2014).

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Jang JY. Methodology: Lee WC. Formal analysis: Jun BG. Data curation: Kim YD, Cho YS, Lee YN. Software: Cheon GJ, Kim HS. Validation: Jeong SW. Investigation: Kim YS. Writing - original draft: Jun BG, Lee SH. Writing - review & editing: Jang JY, Kim SG.

INTRODUCTION

Patients with liver cirrhosis tend to suffer from bacteremia due to the hepatic reticuloendothelial system and neutrophil hypoactivity, coupled with an influx of bacteria into the general circulation via portocaval shunts.[1-3] It is thought that 30%–60% of patients with liver cirrhosis develop a bacterial infection,[3-5] and such infection is involved in one-quarter of deaths among these patients.[6,7]

Spontaneous bacterial peritonitis (SBP) is the most common bacterial infection among liver cirrhosis patients, accounting for at least 24% of infections in that population.[8,9] Although there is a considerable amount of information available regarding the pathogenesis, diagnosis, and treatment of SBP,[8,10] an up-to-date, proven, and easy-to-use clinical factor is not yet available to physicians for determining the in-hospital mortality associated with SBP. The ability to predict prognosis is important with respect to identifying high-risk patients toward whom more intensive monitoring and treatment strategies can be targeted. The predictive model needs to be simple so that it can be easily applied in the real-life, clinical setting. In an attempt to identify independent prognostic factors of in-hospital mortality, a meta-analysis demonstrated that renal dysfunction is a significant independent predictor of prognosis in cirrhotic patients.[11] Unfortunately, that study was limited by no estimation of the optimal cutoff point being reported for the high-risk mortality group.

Early detection of high-risk patients is essential for prognostic improvement. Therefore, finding prognostic factors is important for risk stratification, physician decision making, and individualized medical therapy for different at-risk populations. The establishment of prognostic factors that are modifiable enables early treatment strategies to be developed. Accordingly, the aim of this study was to identify the prevalence and independent predictors of in-hospital mortality in a cohort of liver cirrhosis patients with SBP receiving antibiotics and, if deemed necessary by guidelines, intravenous albumin and terlipressin therapy. A prognostic factor that is easy to implement in real-life, clinical settings was investigated.

METHODS

Patients and procedures

Four hundred and ninety-nine SBP cases occurring between August 2002 and February 2013 were identified. These SBP patients were diagnosed in four tertiary referral hospitals (Soonchunhyang University Seoul Hospital, Bucheon Hospital, Cheonan Hospital, and Gangneng Asan Medical Center), either on hospital admission or during hospitalization due to liver cirrhosis.

The inclusion criteria were as follows: 1) adult patients who were diagnosed with liver cirrhosis based on their clinical presentation, laboratory markers (liver function parameters), and compatible radiology findings (nodular contour to the liver parenchyma and evidence of portal hypertension); 2) diagnosis of SBP based on the presence of an ascitic fluid polymorphonuclear neutrophil (PMN) cell count greater than 250 cells/mm^3 in the absence of any other source of intra-abdominal infection; and 3) diagnostic paracentesis within 24 hours whenever SBP was suspected. Patients were excluded if they had infectious pleural effusion, peritonitis carcinomatosa, malignant ascites, hemorrhagic ascites, septic shock, treatment before ascitic analysis, end-stage renal disease with or without hemodialysis, or previous liver transplantation.

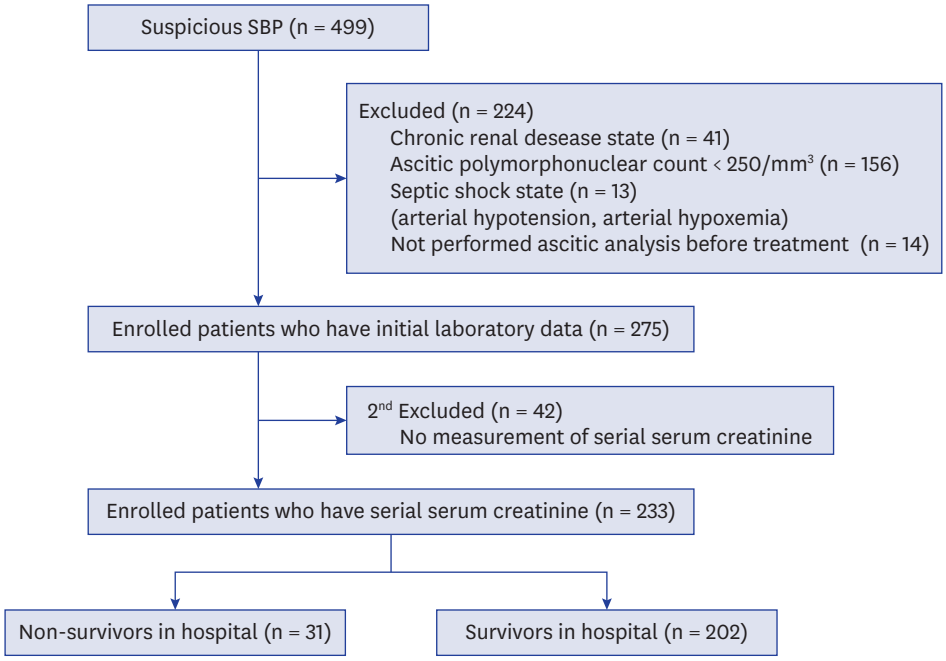

Fig. 1. Disposition of patients in the study.
SBP = spontaneous bacterial peritonitis.

Of the 499 patients initially enrolled with suspicious SBP, 41 patients were excluded as they were in a chronic renal disease state. Another 156 patients were excluded because their ascitic PMN cell count was under 250 cells/mm^3, and 13 were excluded as they were in septic shock with arterial hypotension (systolic blood pressure < 90 mmHg) or arterial hypoxemia (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, < 300), as evidenced by the diagnostic criteria for septic shock.[12] Fourteen patients were excluded because ascitic fluid analysis was not performed before treatment with cefotaxime because of their scanty ascite, and 42 patients were excluded because serial serum creatinine measurements were not available. Ultimately, 233 patients met all of the inclusion criteria (**Fig. 1**).

All the patients were treated with antibiotics. Additionally they were treated with albumin (1 g/kg/day) to prevent hepatorenal syndrome or to supply albumin (1 g/kg/day) if they had a serum albumin level of < 3.0 g/dL based on the guidelines of the Korean National Health Insurance Service.[13,14] All patients with a serum creatinine level of ≥ 2.5 mg/dL were treated with albumin and terlipressin according to the guidelines of the Korean National Health Insurance Service, which were established using the Clinical Practice Guidelines for Liver Cirrhosis, Update, and recommendations from previous studies.[15]

The patients with SBP were divided into non-survivors and survivors in hospital. Information was collected on sex, age, etiology of the cirrhosis, and presence of hepatic encephalopathy. Laboratory variables were obtained at the time of diagnosis, including via serum analysis, via ascitic analysis, and the glomerular filtration rate (GFR) estimated using the Modification of Diet in Renal Disease formula[16,17]:

$$GFR = 170 \times [Pcr]^{-0.999} \times [Age]^{-0.176} \times [0.762 \text{ if patient is female}] \times [1.180 \text{ if patient is black}] \times [BUN]^{-0.170} \times [Alb]^{+0.318}$$

https://doi.org/10.3346/jkms.2018.33.e99

where Pcr is plasma creatinine, BUN is blood urea nitrogen, and Alb is albumin. These data were considered baseline values. Measurement of serum creatinine levels is usually routine upon a diagnosis of SBP and is repeated frequently during the treatment in SBP patients. Therefore, all 233 patients with SBP underwent serial serum creatinine measurement (**Fig. 1**). The Child-Turcotte-Pugh (CTP) and model for end-stage liver disease sodium model (MELD-Na) scores, and serum ascites albumin gradient were calculated using the laboratory data at SBP diagnosis. The prognostic factors related to in-hospital mortality were compared between the two groups (i.e., non-survivors and survivors).

Statistical analysis

The patients' characteristics are described using mean and standard deviation values or proportions. Kaplan-Meier and Cox proportional hazards regression analyses were used to determine independent predictors of in-hospital mortality. The level of statistical significance was set at $P < 0.05$. Variables that have previously been demonstrated to be clinically relevant and/or variables with $P < 0.10$ on univariate analysis were entered into the multivariate model. The results of the binary logistic regression are reported as the odds ratio (OR) and 95% confidence interval (CI). A receiver operating characteristic (ROC) curve was generated for the variables that were statistically significant on multivariate analysis to assess the predictive accuracy of these models and to determine the optimal cutoff points for the prediction of in-hospital mortality. Area under the curve (AUC) analysis was conducted to determine the discriminatory ability of the data. All data were analyzed using the Statistical Package for the Social Sciences (version 17.0, SPSS, Chicago, IL, USA).

Ethics statement

Approval for this study was obtained from Soonchunhyang University Seoul Hospital Institutional Review Board (No. 2013-074). Informed consent was waived by the board.

RESULTS

Characteristics of the patients

In total, 233 patients (181 men and 52 women) were included in the study. The demographic, clinical, and laboratory characteristics of the patients are listed in **Table 1**. The mean age of the patients was 57.1 years. The causes of liver cirrhosis were hepatitis B (44.6%), alcohol (43.8%), hepatitis C (6.0%), and cryptogenic cirrhosis (5.6%). The mean MELD-Na and CTP scores were 27.1 and 10.7, respectively. Fifty-two patients were treated with albumin and terlipressin. Thirty-eight of 52 patients were treated with albumin and terlipressin due to type 1 hepatorenal syndrome at diagnosis and 14 of 52 patients were treated with albumin and terlipressin during the therapeutic period. Eighteen patients (18/52, 34.6%) who were treated with albumin and terlipressin died in hospital with SBP. The in-hospital mortality rate was 14.6% (n = 31) and the mean hospitalization period of non-survivors was 8.3 days. Baseline MELD-Na score ($P = 0.001$), CTP score ($P = 0.005$), absolute neutrophil count ($P = 0.009$), international normalized ratio ($P < 0.001$), ammonia ($P = 0.023$), aspartate transaminase ($P = 0.011$), alanine aminotransferase ($P = 0.001$), GFR ($P = 0.002$), serum creatinine ($P < 0.001$), and maximal serum creatinine ($P < 0.001$) were different between non-survivors and survivors (**Table 2**).

Microbiological characteristics and antibiotics

A profile of the organisms isolated is listed on **Table 3**. Of 233 patients, 29 patients had a positive acsitic fluid culture result: *Escherichia coli* was isolated in 19 patients and *Klebsiella*

https://doi.org/10.3346/jkms.2018.33.e99

Table 1. Baseline demographics of the patients with SBP (n = 233)

Variables	Characteristics
Age, yr	57.1 (11.3)
Male	181 (77.7)
Etiology of cirrhosis	
Alcohol	102 (43.8)
Hepatitis B virus	104 (44.6)
Hepatitis C virus	14 (6.0)
Cryptogenic	13 (5.6)
Hepatic encephalopathy	42 (18.0)
Hepatocellular carcinoma	66 (28.3)
Variceal bleeding	40 (17.2)
Laboratory findings	
Baseline MELD score	22.4 (7.9)
Baseline MELD-Na score	27.1 (7.2)
Baseline CTP score	10.7 (1.9)
Baseline hemoglobin, g/dL	10.3 (2.1)
Baseline ANC, 10^3/μL	11.2 (5.1)
Baseline ammonia, μg/dL	103.4 (79.8)
Baseline total bilirubin, mg/dL	7.1 (7.2)
Baseline INR	2.1 (1.1)
Baseline aspartate transaminase, U/L	122.2 (189.0)
Baseline alanine aminotransferase, U/L	48.4 (81.0)
Baseline CRP, mg/dL	13.0 (27.8)
Baseline platelet, × 10^3/μL	97.6 (69.1)
Baseline GFR, mL/min[a]	58.2 (47.3)
Baseline serum creatinine, mg/dL	1.7 (1.5)
Baseline serum albumin, g/dL	2.4 (0.5)
Baseline ascites albumin, g/dL	0.6 (0.4)
Baseline ascites protein, g/dL	1.4 (1.1)
Baseline SAAG	1.8 (0.5)
Baseline ascite PMN, cells/mm^3	5,722.6 (12,755.1)
Maximal serum creatinine, mg/dL	1.9 (1.6)

Values are presented as number of patients (%) or mean ± standard deviation.
SBP = spontaneous bacterial peritonitis, MELD = model for end-stage liver disease, MELD-Na = model for end-stage liver disease sodium model, CTP = Child-Turcotte-Pugh, ANC = absolute neutrophil count, INR = international normalized ratio, CRP = c-reactive protein, GFR = glomerular filtration rate, SAAG = serum-ascites albumin gradient, PMN = polymorphonuclear neutrophil.
[a]Estimated using the Modification of Diet in Renal Disease formula.

pneumoniae was isolated in 6 patients. Three cases of *E. coli* were resistant to third-generation cephalosporin. Two hundred and thirty-three patients received empirical antimicrobial therapy: 199 (85.4%) received third-generation cephalosporin, 24 (10.3%) received fluoroquinolone, 8 (3.4%) received carbapenem, and 2 (0.8%) received fourth-generation cephalosporin.

Prognostic factors related to in-hospital mortality during treatment

During treatment in hospital, maximum serum creatinine level (OR, 1.776; 95% CI, 1.400–2.254; $P < 0.001$), the absolute neutrophil count (OR, 1.000; 95% CI, 1.000–1.000; $P = 0.015$) and the MELD-Na score (OR, 1.128; 95% CI, 1.062–1.198; $P < 0.001$) were significant prognostic factors of in-hospital mortality on univariate analysis (**Table 2**). The CTP score, total bilirubin, serum albumin, international normalized ratio, ascitic PMN cell count, and hepatic encephalopathy were not statistically significant predictors of in-hospital mortality. Multivariate analysis revealed that the maximum serum creatinine during treatment (OR, 1.680; 95% CI, 1.313–2.151; $P = 0.005$) was an independent predictor of in-hospital mortality (**Table 4**). The follow-up serum creatinine level was significantly higher in non-survivors than survivors (3.6 vs. 1.7 mg/dL).

https://doi.org/10.3346/jkms.2018.33.e99

Table 2. Baseline characteristics between survivors and non-survivors

Variables	Non-survivors (n = 31)	Survivors (n = 202)	*P* value
Age, yr	56.9 (11.1)	57.1 (11.3)	0.950
Male	22 (71.0)	159 (78.7)	0.335
Etiology of cirrhosis			0.112
Alcohol	16 (51.6)	86 (42.6)	
Hepatitis B virus	13 (41.9)	101 (45.1)	
Hepatitis C virus	0 (0)	14 (6.9)	
Cryptogenic	2 (6.5)	9 (4.5)	
Hepatic encephalopathy	8 (25.8)	34 (16.9)	0.231
Hepatocellular carcinoma	10 (32.3)	55 (27.4)	0.572
Variceal bleeding	3 (9.7)	37 (18.3)	0.456
Laboratory findings			
Baseline MELD score	24.9 (7.5)	21.9 (7.8)	0.057
Baseline MELD-Na score	32.1 (6.2)	26.3 (7.0)	< 0.001
Baseline CTP score	11.6 (1.3)	10.5 (1.9)	0.005
Baseline hemoglobin, g/dL	10.2 (2.0)	10.3 (2.1)	0.765
Baseline ANC, 10^3/μL	11,381.5 (7,423.8)	7,808.1 (6,615.9)	0.009
Baseline ammonia, μg/dL	139.1 (118.6)	95.6 (66.9)	0.023
Baseline total bilirubin, mg/dL	9.4 (8.7)	6.7 (6.9)	0.054
Baseline INR	2.87 (1.84)	1.98 (0.87)	< 0.001
Baseline aspartate transaminase, U/L	308.4 (441.9)	93.5 (76.9)	0.011
Baseline alanine aminotransferase, U/L	102.5 (197.2)	40.1 (35.1)	0.001
Baseline CRP, mg/dL	18.7 (34.0)	12.2 (26.8)	0.285
Baseline platelet, × 10^3/μL	105.7 (66.3)	96.3 (69.6)	0.482
Baseline GFR, mL/min[a]	34.0 (31.7)	61.8 (48.2)	0.002
Baseline serum creatinine, mg/dL	2.9 (2.7)	1.5 (1.0)	< 0.001
Baseline serum albumin, g/dL	2.2 (0.4)	2.3 (0.4)	0.285
Baseline ascites albumin, g/dL	0.6 (0.3)	0.5 (0.3)	0.440
Baseline ascites protein, g/dL	1.3 (0.8)	1.8 (0.5)	0.952
Baseline SAAG	1.6 (0.4)	1.8 (0.5)	0.143
Baseline ascite PMN, cells/mm^3	6,688.1 (8,010.9)	5,572.2 (13,348.1)	0.652
Maximal serum creatinine, mg/dL	3.6 (2.7)	1.6 (1.2)	< 0.001

Values are presented as number of patients (%) or mean ± standard deviation.
MELD = model for end-stage liver disease, MELD-Na = model for end-stage liver disease sodium model, CTP = Child-Turcotte-Pugh, ANC = absolute neutrophil count, INR = international normalized ratio, CRP = c-reactive protein, GFR = glomerular filtration rate, SAAG = serum-ascites albumin gradient, PMN = polymorphonuclear neutrophil.
[a]Estimated using the Modification of Diet in Renal Disease formula.

Table 3. Isolated microorganism in SBP

Isolates (n = 29)	No. of patients (%)
Gram-negative organism	
Escherichia coli	19 (65.4)
Klebsiella pneumoniae	6 (20.6)
Enterobacter species	1 (3.5)
Pseudomonas	1 (3.5)
Gram-positive organism	
Staphylococcus aureus	1 (3.5)
Streptococcus species	1 (3.5)

SBP = spontaneous bacterial peritonitis.

Accuracy of prognostic factors related to in-hospital mortality

Multivariate analysis of the prognostic factors related to the in-hospital mortality of SBP patients during treatment revealed that the maximum serum creatinine during treatment was significantly associated with in-hospital mortality. ROC curves were constructed to determine the optimal cutoff points for in-hospital mortality for the remaining variable. A maximum serum creatinine level during treatment of ≥ 2.0 mg/dL had a sensitivity of 77.4%, a specificity of 74.3%, and an AUC of the ROC curve of 0.78 (**Fig. 2**). Thus, patients without

Table 4. Predictors of in-hospital mortality during treatment

Variables	Univariate analysis			Multivariate analysis		
	OR[a]	95% CIs	*P* value	OR[a]	95% CIs	*P* value
MELD	1.046	0.998–1.096	0.060			
MELD-Na	1.128	1.062–1.198	< 0.001	0.941	0.835–1.061	0.332
CTP score	1.405	1.106–1.785	0.005	1.223	0.881–1.724	0.222
Hemoglobin, g/dL	0.973	0.815–1.162	0.764			
ANC, 10^3/μL	1.000	1.000–1.000	0.015	1.000	1.000–1.000	0.109
Total bilirubin, mg/dL	1.040	0.997–1.085	0.069			
INR	1.722	1.280–2.318	< 0.001	1.727	0.993–3.003	0.053
Maximal serum creatinine, mg/dL	1.776	1.400–2.254	< 0.001	1.680	1.313–2.151	0.005
Serum albumin, g/dL	0.636	0.279–1.455	0.284			
Hepatic encephalopathy	1.708	0.705–4.139	0.236			
Ascite PMN, cells/mm^3	1.000	1.000–1.000	0.655			

OR = odds ratio, CI = confidence interval, MELD = model for end-stage liver disease, MELD-Na = model for end-stage liver disease sodium model, CTP = Child-Turcotte-Pugh, ANC = absolute neutrophil count, INR = international normalized ratio, PMN = polymorphonuclear neutrophil.
[a]OR was generated by binary logistic regression.

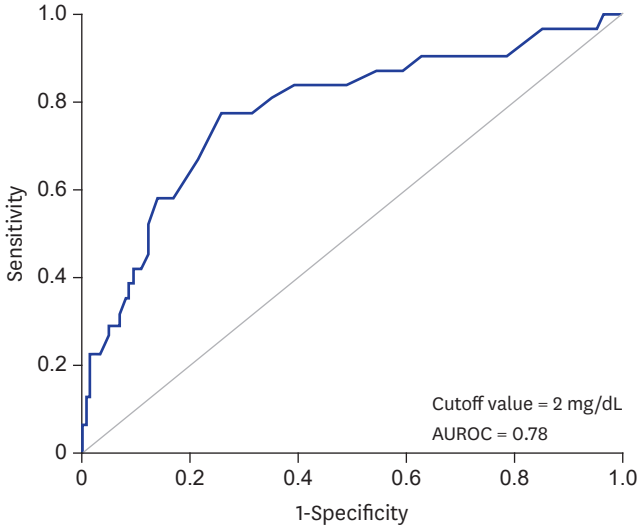

Fig. 2. ROC curve for determining cutoff point for maximal serum creatinine level. A maximal serum creatinine level during treatment of ≥ 2 mg/dL was associated with a sensitivity of 77.4%, a specifity of 74.3%, and an AUROC of 0.78 for determining in-hospital mortality. The solid line represents the ROC based on chance alone and has a c-statistic of 0.5.
ROC = receiver operating characteristic, AUROC = area under ROC curve.

the risk variable had an in-hospital mortality rate of 4.5% (7/157), while those with the risk variable had an in-hospital mortality rate of 31.6% (24/76; **Table 5**). Patients could therefore be divided into high- and low-risk groups according to the maximum serum creatinine cutoff of ≥ 2 mg/dL during treatment, with the survival rate being significantly higher for the low-risk group than for the high-risk group ($P < 0.001$; **Fig. 3**). The mean duration of time during which the level of creatinine rose maximally in patients with maximum serum creatinine level (≥ 2.0 mg/dL) was 4.03 (± 5.938) day.

Table 5. In-hospital mortality determined by the presence of high-risk variable

Variables	In-hospital mortality	Proportion of the group in this category
Maximal serum creatinine ≥ 2 mg/dL	31.6% (24/76)	32.6%
Maximal serum creatinine < 2 mg/dL	4.5% (7/157)	67.4%

https://doi.org/10.3346/jkms.2018.33.e99

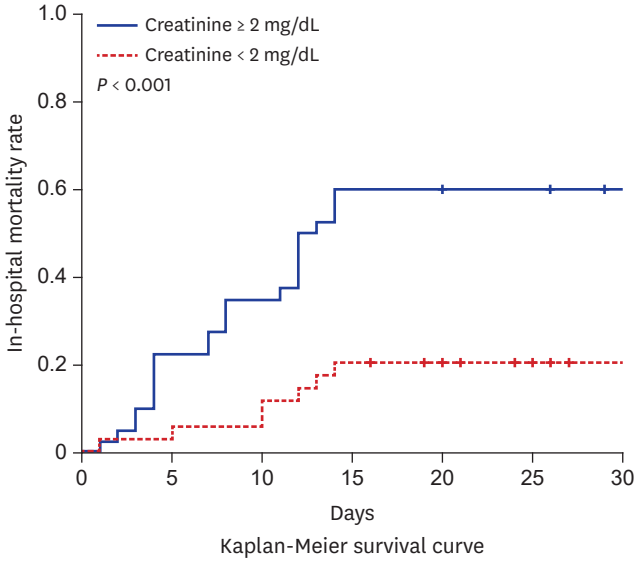

Fig. 3. Mortality rate of cirrhotic patients with SBP. In-hospital mortality rate according to maximal serum creatinine level during treatment. The patients with a maximal serum creatinine level during treatment of ≥ 2 mg/dL showed higher in-hospital mortality rate than a maximal serum creatinine level during treatment of < 2 mg/dL.
SBP = spontaneous bacterial peritonitis.

DISCUSSION

The main findings of the current retrospective study are as follows: 1) renal dysfunction is a robust prognostic factor of patients with cirrhosis and SBP; 2) high serum creatinine levels during treatment are associated with in-hospital mortality; and 3) the optimal cutoff point of maximum serum creatinine during treatment is ≥ 2 mg/dL.

These results are very important because these are based on real-life data. A maximum serum creatinine level during treatment of ≥ 2 mg/dL was the most important predictor of in-hospital mortality in the present cohort. When considering all patients, the absence of this high-risk factor was associated with an in-hospital mortality rate of 4.5%, while its presence was associated with an in-hospital mortality rate of over 30% (**Table 5**).

Renal function has been recognized as an independent predictor of mortality in several clinical settings, including SBP.[11,18-21] The mechanism underlying the association between renal impairment and SBP relative to mortality is probably hemodynamic in nature. Patients with cirrhosis and ascites have a circulatory dysfunction that is characterized by high cardiac output, arteriolar vasodilatation, hypotension, decreased effective arterial blood volume, and homeostatic activation of the renin-angiotensin and sympathetic nervous systems.[22,23] Therefore, the high frequency and severity of renal dysfunction after the onset of SBP are probably due to the combination of the circulation failure already present as an effect of cirrhosis and circulation failure caused by infection.[24,25] This combined effect probably disturbs the compensatory action of renal vasodilators and leads to decreases in renal function that are represented by increased serum creatinine. The finding of the present study that renal impairment is associated with in-hospital mortality can be explained by this hypothesis.

This study was based on patients who had undergone serial serum creatinine measurements and who were classified according to their maximum serum creatinine during treatment.

https://doi.org/10.3346/jkms.2018.33.e99

These data could make it easier to predict the in-hospital mortality of cirrhotic patients with SBP in real-life clinical settings. Terg et al.[26] measured serum creatinine levels 48 hours after treatment in SBP patients, but did not determine the cutoff value, while Soylu et al.[27] used baseline creatinine levels and determined an optimal cutoff value of > 1.1 mg/dL. In addition, a meta-analysis revealed that renal dysfunction defined as a creatinine level of > 1.5 mg/dL is the main prognostic factor of in-hospital mortality in patients with SBP.[28] However, cirrhotic patients with SBP frequently have elevated serum creatinine levels. Therefore, the results of these previous studies have a low discriminatory ability related to the serum creatinine level. The point of difference of the present study is the sense of reality, since maximum serum creatinine levels during treatment reflect the patients' current renal function. Thus, the present results regarding the prediction of in-hospital mortality could be more useful than those published previously. The establishment of a maximum serum creatinine level during treatment of ≥ 2.0 mg/dL is valuable for selecting cirrhotic patients with SBP who are at high risk of in-hospital mortality. In addition, the determined cutoff value (2.0 mg/dL) for the maximum serum creatinine is lower than the diagnostic serum creatinine criterion for type 1 hepatorenal syndrome (2.5 mg/dL).[13,14,29] These findings support the implementation of a serum creatinine level of ≥ 2.0 mg/dL as a predictor of in-hospital mortality in liver cirrhosis patients with SBP. Therefore, physicians should be aware that SBP patients with a maximum serum creatinine level of ≥ 2 mg/dL during treatment have a high risk of in-hospital mortality.

Albumin was administered at 1 g/kg/day to all patients in order to prevent hepatorenal syndrome or when serum albumin was < 3.0 g/dL. Furthermore, albumin (1 g/kg/day) plus terlipressin (1 mg/6 hours) was used only when serum creatinine was ≥ 2.5 mg/dL, in line with the recommendations of the Korean National Health Insurance Service regarding the use of expensive drugs such as albumin and terlipressin. Despite many of the high-risk patients being treated with antibiotics and albumin therapy, SBP mortality rates remained high (over 30%). It is therefore particularly important for physicians to accurately identify high-risk patients at the time of presentation. This encourages vigilance with respect to monitoring and treating these patients and allows more aggressive treatments to be directed toward the high-risk group. The renal dysfunction, and especially the maximum serum creatinine during treatment, should be evaluated for high-risk liver cirrhosis patients with SBP. The results of this study provide physicians with information that should enable them to distinguish cirrhotic patients with SBP who are at high risk of death, thereby allowing them to be managed more intensively.

This study was subject to some limitations: it had a retrospective design and was not a randomized controlled trial. However, the findings reflect circumstances that are closer to real life than would be possible in a planned, randomized controlled trial. Given the still high mortality rates associated with SBP in patients with liver cirrhosis, more research is needed to optimize the therapeutic algorithms for the treatment of this condition. Nevertheless, in the real-life, clinical setting, the use of simple rather than complex prognostic factors, such as that revealed by our results, can aid the physician in identifying high-risk patients toward whom more intensive monitoring and treatment strategies can be targeted.

In conclusion, we suggest that when cirrhotic patients with SBP have a maximum serum creatinine level during treatment of ≥ 2 mg/dL, the physician should identify them as being at high risk of in-hospital mortality, and monitor them intensively to prevent fatal situations such as type 1 hepatorenal syndrome.

https://doi.org/10.3346/jkms.2018.33.e99

REFERENCES

1. Navasa M, Rodés J. Bacterial infections in cirrhosis. *Liver Int* 2004;24(4):277-80.
PUBMED | CROSSREF
2. Johnson DH, Cunha BA. Infections in cirrhosis. *Infect Dis Clin North Am* 2001;15(2):363-71, vii.
PUBMED | CROSSREF
3. Navasa M, Rimola A, Rodés J. Bacterial infections in liver disease. *Semin Liver Dis* 1997;17(4):323-33.
PUBMED | CROSSREF
4. Runyon BA. Bacterial infections in patients with cirrhosis. *J Hepatol* 1993;18(3):271-2.
PUBMED | CROSSREF
5. Caly WR, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. *J Hepatol* 1993;18(3):353-8.
PUBMED | CROSSREF
6. Cheruvattath R, Balan V. Infections in patients with end-stage liver disease. *J Clin Gastroenterol* 2007;41(4):403-11.
PUBMED | CROSSREF
7. Soriano G, Guarner C, Tomás A, Villanueva C, Torras X, González D, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. *Gastroenterology* 1992;103(4):1267-72.
PUBMED | CROSSREF
8. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. *Semin Liver Dis* 2008;28(1):26-42.
PUBMED | CROSSREF
9. Fernández J, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002;35(1):140-8.
PUBMED | CROSSREF
10. Wiest R, Krag A, Gerbes A. Spontaneous bacterial peritonitis: recent guidelines and beyond. *Gut* 2012;61(2):297-310.
PUBMED | CROSSREF
11. Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol* 2011;9(3):260-5.
PUBMED | CROSSREF
12. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;369(9):840-51.
PUBMED | CROSSREF
13. Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007;56(9):1310-8.
PUBMED | CROSSREF
14. Arroyo V, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology* 1996;23(1):164-76.
PUBMED | CROSSREF
15. Sanyal AJ, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology* 2008;134(5):1360-8.
PUBMED | CROSSREF
16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130(6):461-70.
PUBMED | CROSSREF
17. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;31(4):1250-6.
PUBMED | CROSSREF
18. Ariza X, Castellote J, Lora-Tamayo J, Girbau A, Salord S, Rota R, et al. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. *J Hepatol* 2012;56(4):825-32.
PUBMED | CROSSREF
19. Llovet JM, Planas R, Morillas R, Quer JC, Cabré E, Boix J, et al. Short-term prognosis of cirrhotics with spontaneous bacterial peritonitis: multivariate study. *Am J Gastroenterol* 1993;88(3):388-92.
PUBMED

20. Tsung PC, Ryu SH, Cha IH, Cho HW, Kim JN, Kim YS, et al. Predictive factors that influence the survival rates in liver cirrhosis patients with spontaneous bacterial peritonitis. *Clin Mol Hepatol* 2013;19(2):131-9.
PUBMED | CROSSREF

21. Wong F. Acute kidney injury in liver cirrhosis: new definition and application. *Clin Mol Hepatol* 2016;22(4):415-22.
PUBMED | CROSSREF

22. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988;8(5):1151-7.
PUBMED | CROSSREF

23. Moore K, Wendon J, Frazer M, Karani J, Williams R, Badr K. Plasma endothelin immunoreactivity in liver disease and the hepatorenal syndrome. *N Engl J Med* 1992;327(25):1774-8.
PUBMED | CROSSREF

24. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341(6):403-9.
PUBMED | CROSSREF

25. Song HG, Lee HC, Joo YH, Jung S, Park YH, Ryu SH, et al. Clinical and microbiological characteristics of spontaneous bacterial peritonitis (SBP) in a recent five year period. *Korean J Hepatol* 2002;8(1):61-70.
PUBMED

26. Terg R, Cobas S, Fassio E, Landeira G, Ríos B, Vasen W, et al. Oral ciprofloxacin after a short course of intravenous ciprofloxacin in the treatment of spontaneous bacterial peritonitis: results of a multicenter, randomized study. *J Hepatol* 2000;33(4):564-9.
PUBMED | CROSSREF

27. Soylu AR, Dökmeci G, Tezel A, Umit H, Amuca H, Akova M, et al. Predictors of short-term outcome of spontaneous bacterial peritonitis in Turkish cirrhotic patients. *J Gastroenterol Hepatol* 2005;20(4):657-60.
PUBMED | CROSSREF

28. Cereto F, Molina I, González A, Del Valle O, Esteban R, Guardia J, et al. Role of immunosuppression in the development of quinolone-resistant *Escherichia coli* spontaneous bacterial peritonitis and in the mortality of *E. coli* spontaneous bacterial peritonitis. *Aliment Pharmacol Ther* 2003;17(5):695-701.
PUBMED | CROSSREF

29. Martín-Llahí M, Pépin MN, Guevara M, Díaz F, Torre A, Monescillo A, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology* 2008;134(5):1352-9.
PUBMED | CROSSREF