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CLIF–SOFA score and SIRS are independent prognostic factors in patients with hepatic encephalopathy due to alcoholic liver cirrhosis

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Abstract

Hepatic encephalopathy (HE) is a complication associated with worst prognosis in decompensated liver cirrhosis (LC) patients. Previous studies have identified prognostic factors for HE, and recent studies reported an association between systemic inflammatory response syndrome (SIRS) and liver disease. This study aimed to identify prognostic factors for 30-day mortality in alcoholic LC patients with HE who visited the emergency department (ED).

This was a retrospective study of alcoholic LC patients with HE from January 1, 2010, to April 30, 2015. The baseline characteristics, complications of portal hypertension, laboratory values, Child–Pugh class, Model for End-stage Liver Disease (MELD) score, chronic liver failure-sequential organ failure assessment (CLIF–SOFA) score, and SIRS criteria were assessed. The presence of 2 or more SIRS criteria was considered SIRS. The primary outcomes were 30-day mortality and prognostic factors for patients with HE visiting the ED.

In total, 105 patients who met the inclusion criteria were analyzed. Overall, the 30-day mortality rate was 6.7% (7 patients).

Significant variables were hepatorenal syndrome, international normalized ratio, white blood cell count, total bilirubin level, MELD score CLIF–SOFA score, and SIRS in univariate analysis. CLIF–SOFA score and SIRS were the significant factors in the multivariate analysis (hazard ratio 5.56, 15.98; 95% confidence interval 1.18–26.18, 1.58–161.37; $P = 0.03$, $P = 0.02$). The mortality rates differed according to the CLIF–SOFA score ($P < 0.01$).

The CLIF–SOFA score and SIRS in alcoholic LC patients with HE visiting the ED are independent predictors of 30-day mortality.

Abbreviations: ALT = alanine transaminase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CLIF–SOFA = chronic liver failure-sequential organ failure assessment, HE = hepatic encephalopathy, INR = international normalized ratio, LC = liver cirrhosis, MELD = Model for End-stage Liver Disease, SIRS = systemic inflammatory response syndrome.

Keywords: alcoholic, chronic liver failure-sequential organ failure assessment, hepatic encephalopathy, liver cirrhosis, systemic inflammatory response syndrome

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1. Introduction

Hepatic encephalopathy (HE) is a debilitating complication of decompensated liver cirrhosis (LC) that manifests as various neuropsychiatric symptoms.[1,2] Patients with HE use medical facilities more frequently.[2] HE has a worse prognosis than do the other complications of portal hypertension in decompensated LC.[3] Moreover, HE is a predictor of mortality independent of the Model for End-stage Liver Disease (MELD) score in patients with LC.[4–6] Few studies on prognostic factors for HE in LC patients have been performed.

Systemic inflammatory response syndrome (SIRS) has long been used as a marker of the response to inflammation.[7] SIRS is also considered an important factor for prognosis in patients with liver disease,[8–10] and its association with HE in LC has been addressed.[11,12] One study showed that inflammation affects the severity of minimal HE in patients with LC.[12] Another study including patients who were admitted to the intensive care unit (ICU) regardless of etiology showed that SIRS differed between survivors and nonsurvivors in LC patients with severe HE.[13] However, the inflammatory status differs between viral and alcoholic LC.[14] Moreover, the status of patients could change from the time of presentation to the emergency department (ED) to admission to the ICU.

We evaluated the utility of clinical variables in the ED, including scoring systems and SIRS, as predictors of mortality in alcoholic LC patients with HE because they are frequently admitted to the ED.[15] The objective of this study was to identify predictive factors for 30-day mortality in alcoholic LC patients with HE who visited the ED.

2. Patients and methods

2.1. Study design and setting

This was a retrospective study of alcoholic LC patients with HE. This study was conducted in the ED of a tertiary hospital with an annual census of 35,000 patients. The patients were treated by board-certified emergency attending physicians. This study was approved by the Gyeongsang National University hospital institutional review board (number 2015-12-019-001).

2.2. Participants

Patients who visited the ED with LC from January 1, 2010, to April 30, 2015, were considered for inclusion in the study. The inclusion criteria were patients with alcoholic LC who presented with or showed clinical characteristics of HE in the ED. The diagnosis of HE was based on ammonia levels and the clinical characteristics of the patient.[2] Because ammonia levels could be increased in chronic liver disease, high levels only are not diagnosis for HE.[2] Treating physicians identified the symptoms of HEP and other causes changing mental. Abnormal behaviors reported by caregivers were also used to diagnosis. If a patient visited the hospital multiple times, only the first visit during the study period was considered in this study. Patients were excluded if they meet the following criteria: hepatocellular carcinoma, uncertain causes of LC, carrier of chronic viral hepatitis, and symptoms of HE occurring in the ward. Alcohol etiology was based on reported year-long alcohol abuse of >60 g/day for males and >40 g/day for females.[16] Hepatorenal syndrome was defined as the criteria of hepatorenal syndrome by the the International Ascites Club.[17] Spontaneous bacterial peritonitis were defined as elevated neutrophil count in ascitic fluid (>250 cells/mm^3) and/or positive bacterial culture of ascitic fluid.[18]

Table 1

Child–Pugh classification.*

	1 point	2 points	3 points
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time prolongation (s)	1–3	4–6	>6
Ascites	None	Mild	Refractory
Encephalopathy	None	Mild (grade 1–2)	Severe (grade 3–4)

* Child–Pugh classes: A, 5–6 points; B, 7–9 points; C, 10–15 points.

2.3. Data collection

The electronic medical records of the enrolled patients were reviewed. The data were collected using standard patient record forms. Baseline characteristics—such as age, sex, diabetes mellitus, hypertension, alcohol abstinence, dialysis, and a transjugular intrahepatic portosystemic shunt—were assessed. Alcohol abstinence was defined as not consuming alcohol for >1 month. Portal hypertensive complications other than HE—such as varix bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome on presentation—were investigated. The HE grade was categorized according to the West Haven criteria.[2] Grades 1 and 2 were categorized as low grade and grades 3 and 4 as high grade. Ascites was classified as controlled or uncontrolled. The following laboratory values, which are routinely tested in the ED, were assessed: white blood cell count (WBC), platelet count, international normalized ratio (INR), levels of hemoglobin, protein, albumin, bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT), sodium, potassium, ammonia, blood urea nitrogen (BUN), creatinine, and C-reactive protein, and pH. The results of cultures from sputum, urine, ascites, and blood collected within 2 days after ED presentation were evaluated. Three scoring systems are identified. The Child–Pugh score was calculated and the class determined (Table 1).[19] The MELD score was calculated from the results at the time of presentation to the ED according to the following formula[20]:

MELD score = $3.8*\log_e$(bilirubin [mg/dL]) + $11.2*\log_e$ (INR) + $9.6*\log_e$ (creatinine [mg/dL]) + 6.4* (etiology: 0 if cholestatic or alcoholic; 1 otherwise).

Chronic liver failure-sequential organ failure assessment (CLIF–SOFA) score was calculated as Table 2.[21]

The SIRS was identified based on vital signs at the time of presentation to the ED. The SIRS variables were as follows: heart rate >90 beats per minute; temperature >38°C or <36°C, respiration rate >20 breaths per minute or $PaCO_2$ < 32 mm Hg, and WBC >12,000/mm^3 or < 4000/mm^3, or >10% immature neutrophils.[7] An SIRS score of ≥2 was categorized as SIRS.[7] Death within 30 days after visiting the ED was assessed.

2.4. Outcomes

The primary outcomes were 30-day mortality and prognostic factors for patients with HE visiting the ED.

2.5. Data analysis

The SPSS 21.0 statistical software (SPSS Inc., Chicago, IL) was used for statistical analysis. Continuous variables are presented as means (±SD) and categorical variables as numbers (percentages). Univariate and multivariate Cox proportional hazard analyses were used to identify prognostic factors for 30-day mortality.

Table 2

Chronic liver failure-sequential organ failure assessment (CLIF–SOFA) score.

	0 point	1 point	2 points	3 points	4 points
Bilirubin (mg/dL)	<1.2	≥1.2 to < 2.0	≥2.0 to < 6.0	≥6.0 to < 12	≥12
Creatinine (mg/dL)	<1.2	≥1.2 to < 2.0	≥2.0 to < 3.5	≥3.5 to < 5.0 or use of renal replacement therapy	≥5.0
Hepatic encephalopathy grade	No	I	II	III	IV
international normalized ratio	<1.1	≥1.1 to < 1.25	≥1.25 to < 1.5	≥1.5 to <2.5	≥2.5 Or platelet count $\leq 20^{*}10^{9}$/L
mean arterial pressure (mm Hg)	≥70	< 70	Dopamine ≤5 or dobutamine or terlipressin	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Lung $PaO_2^{*}/FiO_2^{\dagger}$ or $SpO_2^{\ddagger}/FiO_2^{\dagger}$	>400 >512	>300 to ≤400 >357 to ≤512	>200 to ≤300 >214 to ≤357	>100 to ≤200 >89 to ≤214	≤100 ≤89

CLIF–SOFA = chronic liver failure-sequential organ failure assessment.
* Partial pressure of arterial oxygen.
† Fraction of inspired oxygen.
‡ Pulse oximetric saturation.

The variables were divided into 2 groups according to previous studies or the receiver operating characteristic (ROC) curve. Variables with a *P*-value < 0.05 in the univariate analysis, together with other variables considered relevant, were included in the multivariate analysis. A *P*-value < 0.05 was considered to indicate statistical significance. Kaplan–Meier survival curves were generated to evaluate survival according to the CLIF–SOFA score.

3. Results

A total of 1779 patients with LC visited the ED during the 5-year study period. Among them, 1395 patients visited due to problems related to LC other than HE. A further 269 patients were excluded due to a repeat visit to the ED, hepatocellular carcinoma, or nonalcoholic LC. Ten patients who showed symptoms of HE on the ward were also excluded. In total, 105 patients who met the inclusion criteria were enrolled in the study (Fig. 1).

Males accounted for 91.4% of the total patients, and the mean age was 57.8 (± 9.9) years. More than half of the patients still consumed alcohol (53.3%). Forty-seven patients had high-grade HE. Hepatorenal syndrome was found in 6 patients, spontaneous bacterial peritonitis in 4, and variceal bleeding in 11. The baseline characteristics of the patients are shown in Table 3. Cultures were performed in 58 patients, of whom 16 showed positive results. Mean MELD and CTP scores were 13.1 (± 8.5) and 10.8 (± 2.3),

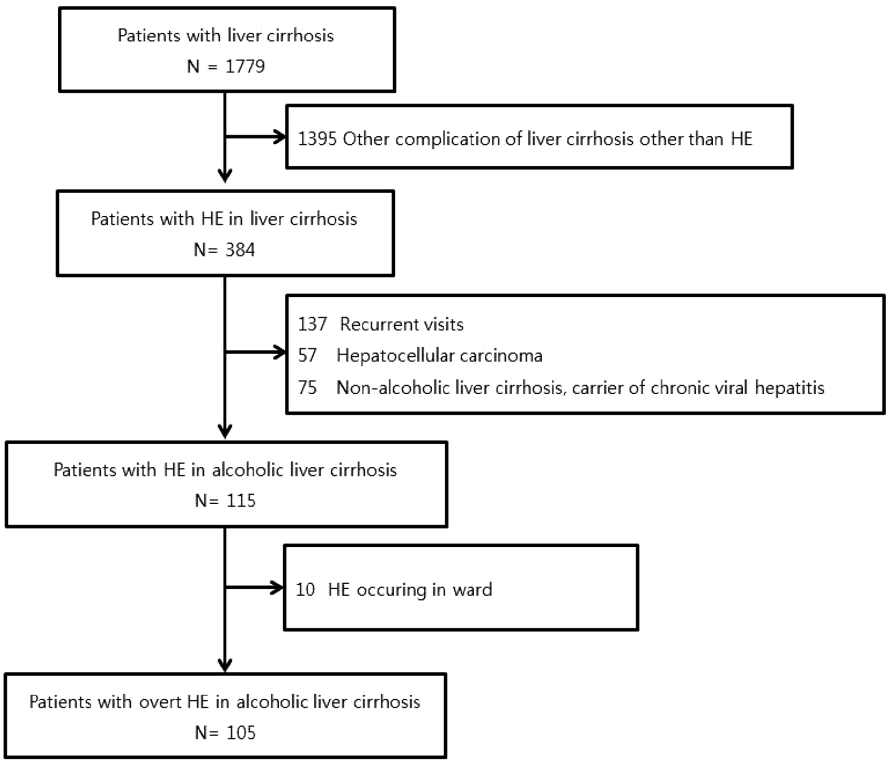

Figure 1. The study patients.

Table 3

Baseline characteristics of the patients.

	Total patients (n = 105)	Surviving patients (n = 98)	Deceased patients (n = 7)	*P*
Age, years (± SD)	57.8 (± 9.9)	58.2 (± 10.1)	51.6 (± 4.4)	<0.01
Male, n (%)	96 (91.4%)	89 (90.8)	7 (100)	0.52
Diabetes mellitus, n (%)	32 (30.5)	31 (31.6)	1 (14.3)	0.31
Hypertension, n (%)	9 (8.6)	9 (9.2)	0 (0)	0.52
Alcohol abstinence, n (%)	49 (46.7)	46 (46.9)	3 (42.9)	0.58
Dialysis, n (%)	1 (1.0)	1 (1.0)	0 (0)	0.93
Transjugular intrahepatic portosystemic shunt, n (%)	2 (1.9)	2 (2.0)	0 (0)	0.87
Grade of HE, n (%)				0.03
Low	58 (55.2)	57 (58.2)	1 (14.3)	
High	47 (44.8)	41 (41.8)	6 (85.7)	
Uncontrolled ascites, n (%)	30 (28.6)	26 (26.5)	4 (57.1)	0.10
Hepatorenal syndrome, n (%)	6 (5.7)	4 (4.1)	2 (28.6)	0.05
Spontaneous bacterial peritonitis, n (%)	4 (3.8)	3 (3.1)	1 (14.3)	0.24
Variceal bleeding, n (%)	11 (10.5)	10 (10.2)	1 (14.3)	0.55
Child–Pugh class, n (%)				0.06
A and B	34 (32.4)	34 (34.7)	0 (0)	
C	71 (67.6)	64 (65.3)	7 (100)	

HE = hepatic encephalopathy, SD = standard deviation.

respectively. The mean CLIF–SOFA score was 7.7 (±2.5). All of the patients were treated with lactulose; enemas were performed in the majority of patients.

Overall, the 30-day mortality rate was 6.7% (7 patients). Clinical and laboratory variables—age, gender, diabetes mellitus, hypertension, alcohol abstinence, dialysis, transjugular intrahepatic portosystemic shunt, HE grade, ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, variceal bleeding, laboratory results (WBC count, platelet, INR, levels of hemoglobin, protein, albumin, total bilirubin, AST, ALT, sodium, potassium, ammonia, BUN, creatinine, and C-reactive protein, pH and culture results), Child-Pugh class, MELD score, CLIF–SOFA score and SIRS —were compared by univariate Cox regression analysis. Of these factors, hepatorenal syndrome, WBC, INR, total bilirubin level, MELD score, CLIF–SOFA score, and SIRS were found to be significant (Table 4, Supplemental Digital Content, http://links.lww.com/MD/B36). Among them, we assumed inter-correlations between significant variables; therefore, we selected CLIF–SOFA score and SIRS for multivariate Cox regression to identify independent prognostic factors for 30-day mortality. These factors were adjusted for age, gender, alcohol abstinence, and culture results. CLIF–SOFA score and

Table 4

Univariate Cox proportional hazard models for 30-day mortality.

	Surviving patients (n = 98)	Deceased patients (n = 7)	Hazard ratio	95% CI	*P*
Hepatorenal syndrome					
No	94 (95.9)	5 (71.4)	1		
Yes	4 (4.1)	2 (28.6)	6.45	1.25–33.31	0.03
SIRS*, n (%)					
No	72 (73.5)	1 (14.3)	1		
Yes	26 (26.5)	6 (85.7)	15.40	1.85–127.96	0.01
MELD† score, n (%)					
< 20	84 (85.7)	2 (28.6)	1		
≥ 20	14 (14.3)	5 (71.4)	11.77	2.28–60.73	<0.01
International normalized ratio, n (%)					
< 2.0	84 (85.7)	2 (28.6)	1		
≥ 2.0	14 (14.3)	5 (71.4)	11.77	2.28–60.73	<0.01
White blood cell count, n (%)					
< 12,000/mm^3	87 (88.8)	3 (42.9)	1		
≥ 120000/mm^3	11 (11.2)	4 (57.1)	8.30	1.85–37.23	<0.01
Total bilirubin, n (%)					
< 10 mg/dL	82 (83.7)	3 (42.9)	1		
≥ 10 mg/dL	16 (16.3)	4 (57.1)	5.90	1.32–26.39	0.02
CLIF–SOFA‡ score					
< 12	91 (92.9)	3 (42.9)	1		
≥ 12	7 (7.1)	4 (57.1)	12.51	2.79–56.19	<0.01

CI = confidence interval, CLIF–SOFA = chronic liver failure-sequential organ failure assessment, MELD = model for end-stage liver disease, SIRS = systemic inflammatory response syndrome.

* Systemic inflammatory response syndrome.

† Model for end-stage liver disease.

‡ Chronic liver failure-sequential organ failure assessment.

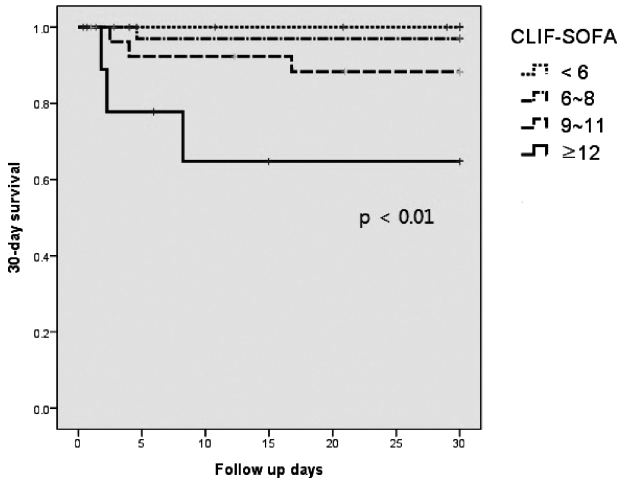

Figure 2. Survival according to the CLIF–SOFA score. CLIF–SOFA = chronic liver failure-sequential organ failure assessment.

SIRS were significant factors (hazard ratio 5.56, 15.98; 95% confidence interval 1.18–26.18, 1.58–161.37; $P = 0.03$, $P = 0.02$). Survival according to the CLIF–SOFA score was evaluated by Kaplan–Meier analysis (Fig. 2); higher CLIF–SOFA scores were associated with higher 30-day mortality rates ($P < 0.01$).

4. Discussion

In this study, the 30-day mortality rate of alcoholic LC patients with HE was 6.7%, and the CLIF–SOFA score and SIRS were significant factors. Patients with higher CLIF–SOFA had a higher 30-day mortality rate.

Previous studies have reported that systolic blood pressure, MELD score, WBC, electrolytes, HE grade, renal function, and ammonia level are significant prognostic factors for HE.[5,22–27] These studies included patients regardless of the etiology of LC, such as viral infection or alcohol consumption; however, the clinical features of LC differ according to the etiology of the condition.[16,28,29] The clinical outcomes and prognosis of patients with alcoholic LC have been reported.[27,30–32] Limited studies on alcoholic LC patients with HE have been performed, and the results indicated that treatment should take place in the ICU.[33] This is, to our knowledge, the first study on prognostic factors for alcoholic LC patients with HE.

The CLIF–SOFA score was developed for acute decompensation of cirrhosis.[21] Acute decompensation is defined as acute development of major complication such as HE, ascites, gastrointestinal bleeding, and bacterial infection.[21] The SOFA score and CLIF–SOFA score were differed in coagulation and cerebral components.[21] Because hypersplensim by portal hypertension in LC cause sequestration of platelets, platelet is replaced by INR in coagulation component.[34] And cerebral component is changed from the Glasgow Coma Score to HE grade because of difficulties of assessment for lower grade of HE.[34] Other studies for all causes of LC validated its effectiveness for prognosis.[34,35] One study for the patients with alcoholic LC also validated scoring systems and showed that CLIF–SOFA could predict the 4-week mortality more accurate than other scoring systems.[36] Our study also showed CLIF–-SOFA was a significant factor for 30-day mortality. Physician can easily calculated the CLIF–SOFA score and predict the prognosis.

SIRS is an uncontrolled inflammatory response.[7] An SIRS and the presence of infection are criteria used to define sepsis. Because the liver plays a major role in the response to infection, patients with liver disease are prone to infection.[37] Therefore, the relationship between SIRS and liver disease has been investigated for >10 years.[8] Rolando et al. reported that SIRS was associated with a poorer prognosis in acute liver failure.[8] Recent studies have also suggested that SIRS has a prognostic value in acute liver failure.[38] Chronic liver diseases are also associated with SIRS.[13,39] Michelena et al reported SIRS to be related to 90-day mortality in patients with alcoholic hepatitis.[39] These studies showed that SIRS is significantly associated with a poorer prognosis, irrespective of the presence of infection.[8,13,38,39] Our results also indicated that infection was not associated with 30-day mortality, possibly related to sterile inflammation in liver disease.[40] Sterile inflammation is an inflammatory response to stimuli in the absence of pathogens.[40] Studies have shown that sterile inflammation plays a role in alcoholic liver disease, nonalcoholic liver disease, and drug-induced liver injury.[40,41] Endogenous damage-associated molecular patterns released from damaged cells trigger an inflammatory response, resulting in immune-mediated fibrosis of the liver.[40] This sterile inflammation might be related to SIRS. In some cases, however, it is difficult to identify the site of infection, and the culturing of some pathogens requires a prolonged period. The availability of laboratory results also can take several hours. In contrast, the SIRS can be calculated within a few minutes and is thus a suitable initial prognostic factor for mortality in the ED.

Wong et al showed that the addition of HE to the MELD score increased its prognostic value, and the adjusted score was used to prioritize patients awaiting liver transplantation.[5] Our results will assist identification of more urgent cases and patients who require more aggressive treatment, such as liver transplantation. As mortality differed according to the CLIF–SOFA score, it might be possible more selective choices for treatment.

This study had several limitations. First, because this was a retrospective study, data regarding some variables, such as culture results and precipitating factors, were missing for a proportion of the patients. Because the presence of infection was reported previously not to be a significant factor, the absence of culture results likely did not influence our findings. Predicting mortality based on the present status of the patients is crucial, regardless of the precipitating factors. Second, we did not compare patients with LC due to other causes. Third, alcohol abstinence might be a related factor; however, this information may have been erroneous as the patients provided the data. Fourth, this study was conducted at a single center. Therefore, further prospective and multicenter studies should be conducted.

5. Conclusion

In conclusion, the CLIF–SOFA score and SIRS in alcoholic LC patients with HE visiting the ED are independent predictors of 30-day mortality.

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