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The Usefulness of Serum Ferritin Level for Evaluating Clinical Outcomes in Cirrhotic Patients with Sepsis

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ABSTRACT

Background: Ferritin is an acute phase reactant and the cellular storage protein for iron. Liver cirrhosis and sepsis increase the levels of proinflammatory cytokines and stimulate ferritin synthesis resulting in rising levels of serum ferritin. Raised serum ferritin concentration was shown to predict mortality and liver related clinical complications in patients with decompensated cirrhosis. The present study was aimed to evaluate the utility of baseline and serial measurements of serum ferritin for predicting mortality and morbidity in hospitalized cirrhotic patients with sepsis.

Methods: This prospective study was conducted at a tertiary care center (Rajavithi Hospital, Bangkok) between March 2015 and November 2015. Thirty cirrhotic patients with sepsis of various types and sites of infection were enrolled. Serum ferritin levels were tested at the time of admission (D1) and on the fifth day of admission (D5). Serum transferrin saturation was collected at base line. Liver-related morbidity was defined as the development of hepatic encephalopathy, spontaneous bacterial peritonitis, variceal bleeding and/or hepatorenal syndrome during admission.

Results: Thirty cirrhotic patients with sepsis were included, 57% male with a median age of 53 years. The mean serum ferritin levels on D1 and the mean ratio of serum ferritin D1/D5 between patients who died (1224.6 µg/L vs. 3237.2 µg/L; p=0.529) and those who survived (1.05 vs. 2.39, p=0.719) were not statistically significantly different. The mean transferrin saturation rates in patients who died were significantly higher than in those who survived (65.38% vs. 34.41%, p=0.012). In patients with serum transferrin saturation <30% (n=11), 81.8% (9/11) survived and 18.2% (2/11) died during hospitalization (p=0.045), whereas in patients with serum transferrin saturation ≥30% (n=19), 42.1% (8/19) survived and 57.9% (11/19) died during hospitalization (p=0.045).

Conclusion: Serum ferritin level did not predict clinical outcomes in terms of mortality and complications in cirrhotic patients with sepsis. However, high serum transferrin saturation ≥30% was associated with a high mortality and could serve as an early predictor of mortality in cirrhotic patients with sepsis.

Key words : Ferritin, mortality, sepsis, infection, cirrhosis

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INTRODUCTION

Cirrhosis is a multifactorial immunocompromised state which predisposes the patient to a variety of infections[1]. Once an infection occurs, excessive proinflammatory cytokines and hemodynamic circulation derangement further facilitate the development of serious consequences of infections such as septic shock, multiple organ failure and death. To date, sepsis remains very common and causes significant morbidity and mortality, accounting for approximately 30% of deaths among cirrhotic patients[2,3].

Several scoring systems, such as MELD score, SOFA score, CLIF-SOFA, APACHE score[4,5], have been evaluated to predict mortality of cirrhotic patients with a critical illness. Although their accuracies are acceptable, these scores require multiple input parameters and computerized calculation. Thus, the search for predicting models that are more accurate and easy-to-use, such as a single laboratory test, is still ongoing.

One example of serum acute phase reactant protein that increases rapidly as the inflammatory response in the cirrhotic patient with infection is c-reactive protein (CRP). During an infection, CRP level is typically elevated, and a decrease in CRP level predicts clinical improvement, whereas a persistently elevated CRP level indicates a poor clinical outcome[6,7].

Ferritin is an acute phase reactant and the cellular storage protein for iron. It composes of 24 protein subunits that play a major role in iron requirement regulation[8]. The normal range of serum ferritin level and its half-life are 50-200 ng/mL and 7-30 hr respectively[9]. Serum ferritin increases in patients who have elevated body iron stores, hepatic necroinflammatory activity and systemic inflammatory states[10,11]. When sepsis develops, proinflammatory cytokines, such as interleukin 6, interleukin 8, and tumor necrosis factors, are markedly released, especially in the early phase. Consequently, the increased proinflammatory cytokines stimulate ferritin synthesis, resulting in a rising level of serum ferritin. In adults with critical illness, ferritin levels range from 471 - 1,536 ng/mL, which are much higher than normal[12,13].

Hyperferritinemia in chronic liver disease has been observed primarily in hereditary hemochromatosis and in conditions with secondary iron overload, such as in patients with the metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), alcohol-related and viral-related chronic liver diseases. In patients with NAFLD[14] studies have shown that in patients without iron accumulation in the liver, an elevated ferritin concentration rather than iron overload itself is more reflective of histological damage[15]. Recently, raised serum ferritin concentration was shown to predict mortality and liver related clinical complications in patients with decompensated cirrhosis awaiting liver transplantation. In addition, a previous study in 318 hospitalized patients with decompensated cirrhosis demonstrated that serum ferritin levels correlated with severity of hepatic decompensation and were associated with early liver-related death independent of the MELD score[16].

Nevertheless, there has been no study evaluating serum ferritin as an early indicator of mortality in cirrhotic patients with sepsis. This study was aimed to evaluate the utility of baseline and serial measurements of serum ferritin for predicting mortality and morbidity in hospitalized cirrhotic patients with sepsis.

Patients and Method

This prospective study was conducted to evaluate the role of serum ferritin in cirrhotic patients with sepsis admitted at a tertiary care hospital (Rajavithi Hospital, Bangkok). The study was conducted between March 2015 and November 2015, and was approved by the Clinical Research Ethics Committee of Rajavithi Hospital (58019). All patients gave informed consent before entering the study.

Inclusion criteria were (1) age 18-80 years; (2) diagnosis of cirrhosis established by acceptable clinical, laboratory and imaging standards or by liver biopsy; and (3) presentation with sepsis, defined according to the criteria of the American College of Chest Physicians/ Society of Critical Care Medicine (ACCP/ SCCM) consensus conference[17]. Exclusion criteria were (1) patients with hemochromatosis or hemophagocytic lymphohistiocytosis; (2) patients with chronic renal failure (stage 3); (3) patients with gastrointestinal tract bleeding at admission; (4) patients with advanced hepatocellular carcinoma (Barcelona Clinic Liver Cancer stage C or above); and (5) patients who had prior history of non-hepatic malignancy.

Clinical and laboratory data were prospectively collected, including age, sex, vital signs, physical examination, type of infection and microorganism, Child-Turcotte-Pugh score (CTP score) at admission, Model for End-Stage Liver Disease (MELD) score at admission, length of stay, and hospital mortality within 30

days of follow up. Liver-related complications were defined as the development of hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), variceal bleeding and/or hepatorenal syndrome (HRS) during admission.

Serum ferritin analysis

Blood samples for the measurement of ferritin were obtained by venipuncture on the admission day and on day 5-after admission. Standard sampling tubes containing separating gel (Li-, NH_4-heparin, K_2-EDTA and K_3-EDTA plasma) was used to collect the serum samples. Ferritin level was measured by a commercial electrochemiluminescence (ECL) technology measuring unit (Cobas e 602 module, Roche diagnostics).

Statistical analysis

Descriptive statistics (mean, SD, and range), qualitatively expressed by percentage were used to report information. Comparisons between variables were made by using Chi-square for categorical variables and *t*-tests for continuous variables. $p < 0.05$ was regarded as statistically significant. The statistical tests were performed using SPSS version 17.0 and STATA.

Results

Patients' characteristics

A total of 57 cirrhotic patients with sepsis were admitted to the hospital during the study period. Twenty-seven patients were excluded from the study due to chronic renal failure (n=5), gastrointestinal tract bleeding (n=12) or advanced hepatocellular carcinoma (Barcelona Clinic Liver Cancer stage C or above) (n=10).

Baseline characteristics of the 30 cirrhotic patients presented with sepsis are shown in Table 1. Cirrhotic patients (56.7% male) with a median age of 53 years were enrolled to this study. The etiologies of cirrhosis were alcohol abuse (43.3%), hepatitis B infection (13.3%), hepatitis C infection (10%), more than 1 factors such as HBV and HCV coinfection (16.7%) and cryptogenic (16.7%). The most common site of infection was SBP (63.3%) followed by unidentified source of infection (16.7%), respiratory tract infection (10%), UTI (6.7%), primary septicemia (6.7%), hepatobiliary tract infection (3%) and gastrointestinal tract infection (3%).

Materials for microbiological studies were obtained from the suspected sites of infection. The most common site of positive microbiological study was hemoculture that was positive in 11/30 patients (36.7%) (6 *Escherichia coli;* non-ESBL, 1 *Streptococcus bovis,* 1 *Vibrio albensis,* 1 *Staphylococcus aureus,* 1 *Streptococcus viridans* and 1 *Roseomonas mucosa*). Ascites culture was positive in 1/16 patients (6.3%) (*Enterococcus casseliflavus*). Sputum culture was positive in 2/10 patients (20%). Urine culture was positive in 1/30 patients (3.3%). Based on the type of infection, 20 patients (66.7%) were classified as community-acquired, 9 patients (30%) as healthcare-associated, and 1 patient (3.3%) as hospital-acquired.

The mean MELD score was 22. With according to CTP score, 8 patients (26.7%) were classified as CTP class B, and 22 patients (73.3%) were classified as class C. Eight patients (26.7%) were receiving beta-blockers as a prophylactic medication for first variceal bleeding or rebleeding, and 7 patients (23.3%) were taking diuretics for treatment of ascites.

The most common liver-related morbidity after admission was hepatic encephalopathy (HE) (40%), followed by SBP (13.3%) and variceal bleeding (13.3%). Nine patients (30%) were readmitted within 30 days after the first admission, and 13 patients (43.3%) died within 30 days after the first admission.

The 30-day mortality

Of the 13 patients who died in this study, 12 (92.3%) died from infection, the remaining from HRS. The mean serum ferritin levels in the first day of admission (ferritin D1) in patients who died tended to be lower than in those who survived, but not statistically significant (1224.6 μg/L vs. 3237.2 μg/L; p=0.529; Table 1). Similarly, the mean ratio of serum ferritin D1 and D5 after admission (ferritin D1/D5 ratio) in patients who died tended to be lower than in those who survived, but not statistically significant. (1.05 vs. 2.39, p=0.719). There was no significant difference in patients with different baseline serum ferritin levels using cut-off >400 μg/L [9 (69.2%) vs. 12 (70.6%), p=0.936] and cut-off >200 μg/L [10 (76.9%) vs. 14 (82.4%), p=0.713]. The mean transferrin saturation rates in patients who died were significantly higher than in those who survived (65.38% vs. 34.41%, p=0.012). In patients with serum transferrin saturation <30% (n=11), 81.8% (9/11) survived and 18.2% (2/11) died during hospitalization (p=0.045), whereas in patients

Table 1. Demographic, clinical and laboratory data in patients who survived and in patients who died within 30 days after the first admission.

Variables	Total (n=30)	Death (n=13)	Survived (n=17)	OR (95%CI)	*p*-value
Sex					
Male	17 (56.7%)	7 (53.8%)	10 (58.8%)	0.89 (0.39, 2.02)	1.000
Female	13 (43.3%)	6 (46.2%)	7 (41.2%)	1.12 (0.5, 2.54)	1.000
Age (years)	53 ± 16	57 ± 13	51 ± 17	1.027 (0.976, 1.08)	0.305
Length of stay (days)	15 ± 10	16 ± 10	13 ± 10	1.034 (0.957, 1.116)	0.398
Cause of cirrhosis					
Alcohol	13 (43.3%)	6 (46.2%)	7 (41.2%)	1.12 (0.5, 2.54)	1
Hepatitis B	4 (13.3%)	0 (0%)	4 (23.5%)	0 (0, 1)	0.113
Hepatitis C	3 (10%)	2 (15.4%)	1 (5.9%)	1.64 (0.65, 4.11)	0.565
> 1 factors	5 (16.7%)	3 (23.1%)	2 (11.8%)	1.5 (0.63, 3.55)	0.628
Others	5 (16.7%)	2 (15.4%)	3 (17.6%)	0.91 (0.28, 2.9)	1
History of UGIB	6 (20%)	3 (23.1%)	3 (17.6%)	1.2 (0.47, 3.04)	1.000
History of HE	5 (16.7%)	2 (15.4%)	3 (17.6%)	0.91 (0.28, 2.9)	1.000
History of SBP	6 (20%)	4 (30.8%)	2 (11.8%)	1.78 (0.83, 3.82)	0.360
Source of infection					
SBP	16 (53.3%)	7 (53.8%)	9 (52.9%)	1.02 (0.45, 2.32)	1.000
Primary septicemia	2 (6.7%)	1 (7.7%)	1 (5.9%)	1.17 (0.27, 4.98)	1.000
Other	12 (40%)	5 (38.5%)	7 (41.2%)	0.94 (0.4, 2.18)	1.000
Type					
Community	20 (66.7%)	7 (53.8%)	13 (76.5%)	0.58 (0.27, 1.28)	0.255
Healthcare	9 (30%)	5 (38.5%)	4 (23.5%)	1.46 (0.66, 3.24)	0.443
Nosocomial	1 (3.3%)	1 (7.7%)	0 (0%)	2.42 (1.57, 3.73)	0.433
Vital signs					
Heart rate (/min)	107.2 ± 25.86	109.85 ± 19.67	105.18 ± 30.2	1.007 (0.978, 1.038)	0.621
Systolic BP (mmHg)	118.53 ± 19.26	115.08 ± 14.9	121.18 ± 22.1	0.981 (0.94, 1.025)	0.396
Diastolic BP (mmHg)	68.53 ± 11.43	72.15 ± 10.74	65.76 ± 11.46	1.055 (0.984, 1.132)	0.134
Body temperature (Celsius)	38.04 ± 1.88	37.22 ± 2.29	38.67 ± 1.23	0.421 (0.17, 1.042)	0.061
Respiratory rate (/min)	22 ± 4.61	22.92 ± 5.14	21.29 ± 4.18	1.085 (0.917, 1.283)	0.344
Physical Examination					
Pallor	18 (60%)	6 (46.2%)	12 (70.6%)	0.57 (0.25, 1.28)	0.264
Jaundice	21 (70%)	9 (69.2%)	12 (70.6%)	0.96 (0.4, 2.33)	1.000
Ascites					
no	4 (13.3%)	1 (7.7%)	3 (17.6%)	0.54 (0.09, 3.11)	0.613
mild	16 (53.3%)	6 (46.2%)	10 (58.8%)	0.75 (0.33, 1.71)	0.713
mark	10 (33.3%)	6 (46.2%)	4 (23.5%)	1.71 (0.78, 3.75)	0.255

Table 1. Demographic, clinical and laboratory data in patients who survived and in patients who died within 30 days after the first admission.

Variables	Total (n=30)	Death (n=13)	Survived (n=17)	OR (95%CI)	*p*-value
HE (grade)					
0	16 (53.3%)	6 (46.2%)	10 (58.8%)	0.75 (0.33, 1.71)	0.713
1	10 (33.3%)	3 (23.1%)	7 (41.2%)	0.6 (0.21, 1.7)	0.440
2	3 (10%)	3 (23.1%)	0 (0%)	2.7 (1.65, 4.42)	0.070
3	1 (3.3%)	1 (7.7%)	0 (0%)	2.42 (1.57, 3.73)	0.433
4	0 (0%)	0 (0%)	0 (0%)	-	-
CTP score	11 ± 2	12 ± 2	10 ± 2	1.413 (0.951, 2.099)	0.087
A	0 (0 %)	0 (0%)	0 (0%)	-	-
B	8 (26.7%)	2 (15.4%)	6 (35.3%)	0.5 (0.14, 1.78)	0.407
C	22 (73.3%)	11 (84.6%)	11 (64.7%)	2 (0.56, 7.13)	0.407
MELD	22 ± 8	25 ± 4.7	20.3 ± 6.1	1.2 (0.99, 1.44)	0.065
Ferritin (µg/L)					
Day 1	2365.1 ± 6574.6	1224.6 ± 1223.5	3237.2 ± 8681	1.01 (1, 1.01)	0.529
Day 5	1057 ± 1141.6	948.3 ± 1077.1	1133.8 ± 1211.7	1.01 (1, 1.01)	0.662
D1>D5	14 (50%)	7 (63.6%)	7 (41.2%)	2.5 (0.52, 11.93)	0.25
D1/D5	1.86 ± 4.21	1.05 ± 0.48	2.39 ± 5.38	0.76 (0.17, 3.35)	0.719
>400 µg/L	21 (70%)	9 (69.2%)	12 (70.6%)	0.94 (0.19, 4.52)	0.936
>200 µg/L	24 (80%)	10 (76.9%)	14 (82.4%)	0.71 (0.12, 4.3)	0.713
SI (µg/dL)	67.7 ± 45.35	86.85 ± 47.26	53.06 ± 39.08	1.02 (1, 1.04)	0.055
TIBC (µg/dL)	167.43 ± 84.72	143.77 ± 83.53	185.53 ± 83.51	0.99 (0.98, 1)	0.2
Transferrin sat (%)	47.83 ± 30.4	65.38 ± 31.9	34.41 ± 21.68	1.04 (1.01, 1.08)	0.012*
Tsat <30%	11 (36.7%	2 (15.4%)	9 (52.9%	0.16 (0.03, 0.96)	0.045*
Tsat ≥30%	19 (63.3%)	11 (84.6%)	8 (47.1%)	6.19 (1.04, 36.8)	0.045*
Cr (mg/dL)	1.28 ± 0.62	1.38 ± 0.71	1.2 ± 0.55	1.6 (0.47, 5.42)	0.448
WBC ($\times 10^9$/L)	10.545 ± 8.01	9.99 ± 3.843	10.97 ± 10.24	1 (1, 1)	0.739
Plt (× 1,000/µL)	106.57 ± 80.91	123.08 ± 108.22	93.94 ± 51.86	1 (1, 1)	0.356
INR	1.88 ± 0.72	1.84 ± 0.52	1.92 ± 0.86	0.84 (0.29, 2.43)	0.748
Complication after admission					
HE	12 (40%)	10 (76.9%)	2 (11.8%)	5 (1.73, 14.48)	0.001*
SBP	4 (13.3%)	4 (30.8%)	0 (0%)	2.89 (1.7, 4.9)	0.026*
HAP	8 (26.7%)	7 (53.8%)	1 (5.9%)	3.21 (1.54, 6.66)	0.009*
HRS	2 (6.7%)	2 (15.4%)	0 (0%)	2.55 (1.61, 4.03)	0.179
UTI	1 (3.3%)	0 (0%)	1 (5.9%)	0 (1, 1)	1.000
Variceal bleeding	4 (13.3%)	3 (23.1%)	1 (5.9%)	1.95 (0.92, 4.11)	0.290
Septic shock	11 (36.7%)	9 (69.2%)	2 (11.8%)	3.89 (1.56, 9.7)	0.002*
Readmission in 30 days	9 (30%)	3 (100%)	6 (35.3%)	0.7 (0.25, 1.96)	0.691

UGIB=upper gastrointestinal tract bleeding, HE=hepatic encephalopathy, SBP= spontaneous bacterial peritonitis, SI=serum iron, TIBC = total iron blinding capacity, Tsat = transferrin saturation; Values presented as frequency (%), Means. and Odds ratio (95%CI), *P*-value corresponds to Logistic regression analysis.

with serum transferrin saturation ≥ 30% (n=19), 42.1% (8/19) survived and 57.9% (11/19) died during hospitalization (p=0.045).

Other factors associated with a 30-day mortality were hepatic encephalopathy (HE) (10 vs. 2, p=0.01), hospital-acquired pneumonia (HAP) (4 vs. 0, p=0.026), SBP (7 vs. 1, p= 0.09) and septic shock (9 vs. 2, p=0.002).

Serum ferritin level and complications after admission

There was no statistically significant association between serum ferritin level and the overall complications (HAP, UTI, septic shock and liver-related complications) after admission (Table 2). Similarly, there was no statistically significant association between serum ferritin level and liver-related complications (HE, SBP, variceal bleeding and HRS) after admission (Table 3).

Serum ferritin level and correlation parameter

There was no significant correlation between serum ferritin D1, serum ferritin D5 and serial D1/D5 ratio with MELD score, serum creatinine, hematocrit, platelet, INR, serum iron, TIBC, and transferrin saturation (Table 4).

DISCUSSION

In this study, we prospectively evaluated the usefulness of baseline and serial measurements of serum ferritin for predicting outcomes of hospitalized cirrhotic patients with sepsis. The all-cause mortality rate of patients in this study was 43.4%, which was relatively similar to that of a previous study from Spain by Arvaniti et al[3], reporting 1-month mortality of 38% in hospitalized cirrhosis patient with bacterial infection. However, the majority of deaths in our study were directly due to infection (92.3%), which appeared to be a much higher proportion compared with a previ-

Table 2. Factors associated with the overall complication after admission.

Variables	No complication (n=15)	With complication (n=15)	*p*-value
Ferritin			
Day 1	1229.87 ± 1230.48	3500.33 ± 9233.84	0.353
Day 5	1074.87 ± 1068.32	1037.86 ± 1255.92	0.932
D1/D5	2.23 ± 4.96	0.94 ± 0.27	0.473
MELD	19 ± 6	24 ± 9	0.095
Cr (mg/dL)	1.09 ± 0.51	1.47 ± 0.68	0.091

Values presented as mean±SD. *P*-value corresponds to *t*-test.

Table 3. Factors associated with liver-related complications after admission.

Variables	No complication (n=17)	With complication (n=13)	*p*-value
Ferritin			
Day 1	1317.47 ± 1354.65	3735.08 ± 9921.08	0.327
Day 5	1225.88 ± 1349.16	817.75 ± 750.63	0.352
D1/D5	1.08 ± 0.35	3.06 ± 6.71	0.353
MELD	18 ± 7	26 ± 7	0.003*
Cr (mg/dL)	1.07 ± 0.48	1.55 ± 0.69	0.031*

Values presented as mean±SD. *P*-value corresponds to *t*-test.

Table 4. Correlation of serum ferritin D1, serrum ferritin D5 and serial D1/D5 ratio with MELD score, serum creatinine, hematocrit, platelet, INR, serum iron, TIBC and transferrin saturation.

	Ferritin_D1		Ferritin_D5		Ferritin D1/D5	
	r	*p*-value	r	*p*-value	r	*p*-value
MELD	0.205	0.276	0.150	0.439	0.321	0.096
Cr	0.120	0.528	0.072	0.709	0.097	0.625
Hct	0.109	0.568	-0.008	0.967	-0.138	0.483
Plt	0.207	0.273	0.388	0.038	-0.249	0.202
INR	0.026	0.893	-0.066	0.734	0.155	0.432
SI	0.348	0.060	0.093	0.631	0.327	0.089
TIBC	-0.255	0.174	-0.316	0.095	0.166	0.400
Tsat	0.436	0.016	0.294	0.122	0.300	0.121

P-value corresponds to Spearman's rho correlation

ous study in developed country showing infection accounting for about 30-40% of hospital death[1].

A significant association between serum ferritin, either on D1, on D5, or D1/D5 ratio and the 30-day mortality was not demonstrated in our study. Nevertheless, the role of serum ferritin in this setting remained uncertain due to multiple reasons, such as small sample size and possible uncontrolled confounders in this study. Thus, we noted that even the baseline MELD score did not show a significant association with mortality.

Notably, serum transferrin saturation appeared to correlate with the 30-day mortality. This finding was in contradiction with data from a previous study in patients with decompensated cirrhosis without active infection[18]. Weismuller et al. reported that serum ferritin elevation in combination with transferrin saturation <55% before liver transplantation was an independent risk factor for mortality following liver transplantation, suggesting that acute phase mechanisms beyond iron overload might play a prognostic role[18]. Since serum iron is known to be elevated in patients with sepsis and total iron-binding capacity is reduced in patients with cirrhosis, we believe that these may contribute to the elevation of serum transferrin saturation [transferrin saturation = (serum iron level x 100)/ total iron-binding capacity] seen in our study population. Based on our findings, cirrhotic patients with sepsis who have serum transferrin saturation <30% should be considered as a good prognosis subgroup (82% chance to survive and 18% risk of death during hospitalization). Whereas those patients with serum transferrin saturation ≥30% were more likely to have poor outcomes (42% chance to survive and 58% risk of death during hospitalization), and this group of patients may require very careful monitoring and more aggressive therapy.

Limitation

The main limitations of this study were the relatively small number of patients and the unavoidable clinical heterogeneity of cirrhotic patients in the setting of sepsis.

Conclusions

Serum ferritin level did not predict clinical outcomes in terms of mortality and complications in cirrhotic patients with sepsis. However, high serum transferrin saturation ≥30% was associated with a high mortality, and may serve as an early predictor of mortality in cirrhotic patients with sepsis.

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