Original Article

Thai J Gastroenterol 2016
Vol. 17 No. 3
Sep. - Dec. 2016

Role of Plasma N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) Levels in Cirrhotic Patients with Sepsis

Thanomteeranunt J[1]
Bunchorntavakul C[1]
Pongsuthana S[2]

ABSTRACT

Background: Increased plasma levels of N-terminal pro-Brain natriuretic peptide (NT-proBNP) have been identified as predictors of cardiac dysfunction and death in many critical care settings, including congestive heart failure, myocardial infarction, septic shock and severity of cirrhosis. As NT-proBNP has shown to be related to the severity of liver disease, severity of infection and severity of cardiac dysfunction, the aim of the present study was to determine the role of NT-proBNP as a potential predictor of outcome in cirrhotic patients with sepsis.

Methods: This prospective study was conducted at Rajavithi Hospital between January 2015 and January 2016. Thirty cirrhotic patients with sepsis from various types and sites of infection were enrolled. Plasma NT-proBNP levels were tested at the time of admission (D1) and on the fifth day of admission (D5). Electrocardiography (n=28) and echocardiography (n=24) were performed to evaluate the baseline cardiac functions. Liver-related morbidities were defined by the development of hepatic encephalopathy, spontaneous bacterial peritonitis, variceal bleeding and/or hepatorenal syndrome during admission.

Results: Thirty cirrhotic patients with sepsis were included. There were 57% male with a median age of 53 years. The mean NT-proBNP levels on D1 (2,889.3 pg/mL vs. 2,240.1 pg/mL; p=0.089), on D5 (2,416.7 pg/mL vs. 1,186.9, p=0.24), and the mean of the difference of NT-proBNP levels between D1-D5 (297.6 pg/mL vs. -1053.2 pg/mL, p=0.163) were not significantly different between patients who died and those who survived, respectively. Although, there was a trend of higher NT-proBNP levels on D1 and D5 found in patients who died. Significant predictors for liver-related morbidities were higher NT-proBNP levels on D1 (4,161.9 pg/mL vs. 1,266.9 pg/mL, p= 0.019), higher NT-proBNP levels on D5 (3,036.1 pg/mL vs. 786.1 pg/mL, p=0.026), higher baseline MELD score (26 ± 7 vs. 18 ± 7, p=0.003), and higher baseline serum creatinine (1.55 ± 0.69 mg/dL vs. 1.07 ± 0.48 mg/dL, p=0.031). According to the echocardiographic parameters, a lower MV E/A ratio and a higher LVEF were significantly associated with liver-related morbidities (1.19 ± 0.38 vs. 0.85 ± 0.27, p=0.019 and 69.13 ± 5.38% vs. 75.28 ± 3.63%, p=0.008, respectively).

Conclusion: Plasma NT-proBNP level did not predict in-hospital mortality in cirrhotic patients with sepsis. However, a higher plasma NT-proBNP level was associated with the development of liver-related morbidities, suggesting it may be a potentially useful marker for early detection or prediction of complications in cirrhotic patients with sepsis.

Key words : N-Terminal Pro-brain natriuretic peptide (NT-proBNP), mortality, sepsis, cirrhosis

[Thai J Gastroenterol 2016; 17(3):139-148.]

[1]*Division of Gastroenterology and Hepatology,* [2]*Division of Cardiology, Department of Internal Medicine, Rangsit University, Rajavithi hospital, Bangkok, Thailand.*

Address for Correspondence: *Chalermrat Bunchorntavakul, M.D., Division of Gastroenterology and Hepatology, Department of Internal Medicine, Rangsit University, Rajavithi hospital, Bangkok, Thailand.*

INTRODUCTION

In spite of advances over the past decades in the medical care of patients with decompensate liver cirrhosis, bacterial infections in cirrhotic patients remain common and account for significant morbidity and mortality[1]. Cirrhosis is an immunocompromised state which predisposes the patient to a variety of infections[2]. Bacterial infection is responsible for approximately 30-50% of deaths in cirrhotic patients[2-4]. The most common bacterial infections are spontaneous bacterial peritonitis (SBP) (25-31%), urinary tract infection (UTI) (20-25%), pneumonia (15-21%), bacteremia (12%), and soft tissue infections (11%)[1].

Once infection occurs, the pro-inflammatory cytokines and hemodynamic circulation derangement further facilitate the development of serious consequences of infections[3]. The pathophysiology of the exaggerating inflammatory response in cirrhotic patients has been postulated. In the early stage of sepsis, bacteria and their products, particularly lipopolysaccharides, activate toll-like receptor-4, which induces the release of pro-inflammatory cytokines[4,5]. Nitric oxide (NO), a key mediator contributing to a compromised circulation in septic patients, is markedly released in infected cirrhotic patients[4,5]. A pre-existing hyperdynamic circulatory state predisposes devastating consequences from a sepsis-induced NO and cytokine storm, which eventually leads to refractory hypotension, multiorgan failure and death[2,4,5].

The hyperdynamic circulation in cirrhosis is a progressive vasodilatory syndrome that was first recognized clinically in patients with cirrhosis exhibiting "warm extremities, cutaneous vascular spiders, wide pulse pressure, and capillary pulsations in the nail beds".

Progressive vasodilatation (both splanchnic and systemic) is a key factor in the pathogenesis of many of the complications of cirrhosis, prominently in the kidneys. Splanchnic and systemic vasodilatation in cirrhosis is a consequence of portal hypertension and is attributable mostly to nitric oxide overproduction, although other molecules also participate in this complex process. In addition, vasodilatation leads to a decreased effective arterial blood volume (relative hypovolemia) and activation of neurohumoral systems, such as the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, and non-osmotic release of antidiuretic hormone. Relative hypovolemia further leads to sodium and water retention (with ascites formation), increased intravascular volume, increased cardiac output[5] and decreased systemic vascular resistance with normal or low arterial blood pressure, leading to clinical entity called "cirrhotic cardiomyopathy"[6-8].

Pro-B-type natriuretic peptide (proBNP1-108) is a 108-amino acid prohormone secreted from the cardiomyocytes secondary to cardiac wall distension and stretching and neurohumoral activation in response to ventricular volume and pressure overload[6]. Upon its release, the protease Corin cleaves proBNP108 into N-terminal-proBNP (NT-proBNP), a 76-amino acid biologically inert molecule, and BNP, the biologically active counterpart[7]. The presence of BNP may be regarded as counter-regulatory to the actions of the sympathetic and RAAS. Natriuretic peptide secretion leads to natriuresis, vasodilation activation with a concomitant inhibition of the RAAS and adrenergic activity, inhibition of cardiomyocyte hypertrophy, angiogenesis promotion, and delay in the activation of cardiac fibroblasts, all of which result in improved myocardial relaxation[8,9]. Patients with cirrhosis had elevated levels of plasma NT-proBNP, without signs of reduced hepatic degradation of this hormone[10].

Increased plasma levels of natriuretic peptide hormones have been identified as predictors of cardiac dysfunction and death in many critical care settings, including congestive heart failure[11], myocardial infarction[12], septic shock[13-17] and severity of cirrhosis[18-21]. NT-proBNP has been shown to be related to the severity of liver disease, severity of infection and severity of cardiac dysfunction. Therefore, the aim of the present study was to determine the role of NT-proBNP as a potential predictor of outcome in cirrhotic patients with sepsis.

Patients and Method

This prospective analytic single-center preliminary study was conducted to evaluate the role of NT-proBNP in cirrhotic patients with sepsis. The study was conducted at a tertiary hospital (Rajavithi Hospital, Bangkok) between January 2015 and January 2016, and was approved by the Ethics Committee of Rajavithi Hospital (58002). A written informed consent was obtained from all patients or their legal representatives before enrollment.

Fifty-seven adult cirrhotic patients presenting with sepsis defined according to the criteria of the Ameri-

can College of Chest Physicians/ Society of Critical Care Medicine (ACCP/SCCM) consensus conference[22] were included in this study . The diagnosis of liver cirrhosis included a complex set of typical clinical findings including relevant medical history, presenting symptoms, increased prothrombin time, hypoalbuminemia with albumin-globulin inversion, advanced diffuse chronic hepatic lesion on abdominal ultrasound examination, or liver biopsy. Twenty-seven patients with pre-existing significantly impaired left ventricular function, dilated cardiomyopathy, valvular disease, chronic renal failure, acute coronary artery disease, gastrointestinal bleeding or advanced hepatocellular carcinoma (Barcelona Clinic Liver Cancer stage C or above) were excluded from the study.

The collected demographic data of 30 patients (part of the full study) were age, sex, vital signs, physical examinations, type of infection classified as community-acquired [CA], health-care associated infection [HCA] and hospital-acquired [HA]), site of infection[23], Child-Turcotte-Pugh score (CTP score) at admission, Model for End-Stage Liver Disease (MELD) score at admission, length of stay, laboratory values, hospital morbidity, and mortality. Liver-related morbidities were defined as development of hepatic encephalopathy, spontaneous bacterial peritonitis (SBP), variceal bleeding and/or hepatorenal syndrome (HRS) during admission.

Plasma NT-proBNP analysis

Blood samples for the measurement of NT-proBNP were obtained by venipuncture on the day of admission and day-5 after admission. Serum was collected using standard sampling tubes or tubes containing separating gel (Li-, $NH4^-$heparin, $K2^-$EDTA and $K3^-$EDTA plasma). NT-proBNP was measured by a commercial enzyme immunoassay (The Elecsys proBNP II STAT, Roche diagnostics). The measuring range was 5-35,000 pg/mL, defined by the limit of detection and the maximum of the master curve. Values below the limit of detection were reported as < 5 pg/mL. The values above the measuring range were reported as > 35,000 pg/mL or up to 70,000 pg/mL for 2-fold diluted samples.

Electrocardiogram and Echocardiographic assessments

Electrocardiogram (ECG) was recorded enrollment. The QT interval was assessed on the ECG (25-50 mm/s), its length measured at a stable isoelectric line from the beginning of the QRS complex to the end of the T wave. QT intervals were corrected (QTc) using Bazett's formula, $QTc = QT\ (RR)^{1/2}$, where RR was the R-R interval in seconds. Prolonged QTc interval was defined as $QTc > 0.440\ s^{1/2}$[20].

Echocardiography was performed by an experienced cardiologist using a GE LOGIQ ultrasound, interfaced with a 3S-RS with 1.5-4 MHz transducer probe. The left ventricular ejection fraction (LVEF) was calculated by using the area-length formula[20]. Assessment of diastolic dysfunction was mode in accordance with the recommendations for the Evaluation of Left Ventricular Diastolic Function by EAE/ASE, taking into consideration mitral E, E/A, e' and E/e' ratio[24].

Statistical analysis

For quantitative variables, the mean (SD) or the median (IQR, interquartile range) were used. Qualitative variables were expressed as percentages. Comparisons between variables were made using Chi-square for categorical variables and t-tests for continuous variables. The cut-off value of NT-proBNP was calculated from the ROC (receiver operating characteristics) curve, and the best accuracy of cut-off values was chosen. Logistic regression analysis and multivariate analysis were used to construct the model to predict mortality likelihood for each patient. The ROC curve was used to compare the performance of mortality prediction. $P < 0.05$ was regarded as statistically significant. All statistical tests were performed using SPSS version 17.0 and STATA.

RESULTS

The baseline characteristics of the enrolled cirrhotic patients with sepsis are shown in Table 1. There were 30 cirrhotic patients (56.7% male) with a median age of 53 years. The etiologies of cirrhosis were alcohol abuse (43.3%), hepatitis B infection (13.3%), hepatitis C infection (10%), more than 1 factors, e.g. HBV and HCV co-infection (16.7%), and cryptogenic (16.7%). The most common 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 com-

mon positive microbiological study was hemoculture, being positive in 11 of 30 patients or 36.7% (6 *Eschirichia coli;* non-ESBL, 1 *Streptococcus bovis,* 1 *Vibrio albensis,* 1 *Staphylococcus aeureus,* 1 *Streptococcus viridans* and 1 *Roseomonas mucosa*). Ascites culture was positive in 1 of 16 patients *(Enterococcus casseliflavus).* Sputum culture was positive in 2 of 10 patients (20%). Urine culture was positive in 1 of 30 patients (3.3%). Regarding the types of infection, 20 patients (66.7%) were classified as CA, 9 patients (30%) as HCA, and 1 patient (3.3%) as HA.

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

The most common liver-related morbidities 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 admission.

The 30-day mortality

Of the 13 patients who died, 12 (92.3%) died directly from their infection, the remaining died from HRS. The mean NT-proBNP plasma levels in the first day of admission (NT-proBNP D1) in patients who died were higher than in those who survived, but the difference was not statistically significant (2,889.3 pg/mL vs. 2,240.1 pg/mL; $p = 0.089$), (Table 1). Similarly, the mean of NT-proBNP at day-5 after admission (NT-proBNP D5) and the mean of the difference between NT-proBNP D1 and NT-proBNP D5 (ΔNT-proBNP) were not statistically significant between patients who died and patients who survived (2,416.7 pg/mL vs. 1,186.9, $p = 0.24$ and 297.6 pg/mL vs. -1,053.2 pg/mL, $p = 0.163$, respectively). Other significant factors associated with mortality within 30 days were HE (10 vs. 2, $p = 0.01$), HAP (4 vs. 0, $p = 0.026$), SBP (7 vs. 1, $p = 0.09$) and septic shock (9 vs. 2, $p = 0.002$), which were all classified as morbidities after admission.

EKG and QTc measurements were performed in 28 patients, showing no statistical differences between the non-survival and the survival groups in terms of the mean of QTc (486.42 $ms^{1/2}$ vs. 486 $ms^{1/2}$, $p = 0.984$) and the percentages of patients with prolonged QTc (75% vs. 87.5%, $p = 0.401$). Echocardiography was performed in 24 patients. The mean septal/lateral e' ratio, E/e' ratio, MV E/A ratio, LVEF and diastolic dysfunction were measured, none being significantly associated with survival (Table 1).

Relationship between NT-proBNP plasma level and prognostic outcome

The ROC curve of NT-proBNP D1, the ΔNT-proBNP and the MELD score for determination of mortality in cirrhotic patients with sepsis were not significantly different. The area under the curve (AUC) for the NT-proBNP D1, (20%) the ΔNT-proBNP and the MELD score were 0.62 (95% CI, 0.39 - 0.84), 0.56 (95% CI, 0.32 - 0.80) and 0.61 (95% CI, 0.37 - 0.84), respectively (Figure 1).

Factors associated with morbidities after admission

During the admission period, the occurrence of liver-related morbidities was common in cirrhotic patients with sepsis, especially HE (40%), SBP (13.3%) and variceal bleeding (13.3%). NT-proBNP D1 (1,266.94 ± 2,136.12 pg/mL vs. 4161.92 ± 4148.37 pg/mL, $p = 0.019$), NT-proBNP D5 (786.12 ± 1,659.76 pg/mL vs. 3,036.09 ± 3,375.07 pg/mL, $p = 0.026$), MELD score (18 ± 7 vs. 26 ± 7, $p = 0.003$) and serum creatinine (1.07 ± 0.48 mg/dL vs. 1.55 ± 0.69 mg/dL, $p = 0.031$) were significantly higher in patients with liver-related morbidities compared to those without. Based on echocardiographic parameters, patients with lower MV E/A ratio and higher LVEF were more likely to develop liver-related morbidities (1.19 ± 0.38 vs. 0.85 ± 0.27, $p = 0.019$ and 69.13 ± 5.38 % vs. 75.28 ± 3.63 %, $p = 0.008$; respectively), (Table 2).

Factors associated with NT pro-BNP plasma levels in cirrhotic patients with sepsis

According to the Spearman's rho correlation analysis in cirrhotic patients with sepsis, NT-proBNP D1 plasma levels were positively correlated with the severity of liver disease (higher MELD score), severity of the renal impairment (higher serum creatinine level), and the MV E/A ratio (one of diastolic dysfunction parameters), but not with the diastolic dysfunction itself. Similarly, NT-proBNP D5 was positively correlated with the severity of liver and the severity of

Table 1. (continue) Demographic, clinical and laboratory data in the survival and the non-survival groups within 30 days after the first admission.

Variables	Total (n=30)	Non-survival (n=13)	Survivor (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
More than 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
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					
Pale	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					
0	4 (13.3%)	1 (7.7%)	3 (17.6%)	0.54 (0.09, 3.11)	0.613
1	16 (53.3%)	6 (46.2%)	10 (58.8%)	0.75 (0.33, 1.71)	0.713
2	10 (33.3%)	6 (46.2%)	4 (23.5%)	1.71 (0.78, 3.75)	0.255
HE					
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

Table 1. Demographic, clinical and laboratory data in the survival and the non-survival groups within 30 days after the first admission.

Variables	Total (n=30)	Non-survival (n=13)	Survivor (n=17)	OR (95%CI)	*p*-value
MELD	21.8 ±7.8	22.2 ± 8.2	21.4 ± 7.6	1.01 (0.92, 1.12)	0.771
Site 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
Others	12 (40%)	5 (38.5%)	7 (41.2%)	0.94 (0.4, 2.18)	1.000
Type of infection					
CA	20 (66.7%)	7 (53.8%)	13 (76.5%)	0.58 (0.27, 1.28)	0.255
HCA	9 (30%)	5 (38.5%)	4 (23.5%)	1.46 (0.66, 3.24)	0.443
HA	1 (3.3%)	1 (7.7%)	0 (0%)	2.42 (1.57, 3.73)	0.433
WBC ($\times 10^9$/L)	10.55 ± 80.10	99.92 ± 38.43	10.97 ± 10.24	1 (1, 1)	0.739
NT-proBNP (pg/mL)					
D1	2521.4 ± 3430.4	2889.3 ± 3138.2	2240.1 ± 3707.8	1.01 (0.99, 1.02)	0..616
D5	170 ± 2665.3	2416.7 ± 3534.1	1186.9 ± 1884.1	1 (1, 0.1)	0.240
Δ (D5-D1)	-522.5 ± 2480.3	297.6 ± 2125.6	-1053.2 ± 2606.9	1 (1, 0.1)	0.163
Cr (mg/dL)	1.28 ± 0.62	1.38 ± 0.71	1.2 ± 0.55	1.6 (0.47,5.42)	0.448
Morbidity 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*
EKG (n=28)					
QTc ($ms^{1/2}$)	486.18 ± 55.53	486.42 ± 52.75	486 ± 59.25	1 (0.99, 1.01)	0.984
Prolong QTc	23/28 (82.1%)	9/12 (75%)	14/16 (87.5%)	0.43 (0.06, 3.09)	0.401
Echocardiography (n=24)					
E/e' ratio	10.12 ± 3.76	9.71 ± 4.67	10.32 ± 3.37	0.95 (0.75, 1.21)	0.702
MV E/A ratio	1.08 ± 0.38	0.99 ± 0.37	1.12 ± 0.39	0.37 (0.03, 4.36)	0.428
LVEF (%)	71.18 ± 5.63	74.19 ± 4.61	69.68 ± 5.61	1.18 (0.98, 1.41)	0.074
Diastolic dysfunction	19/25 (79.2%)	6/8 (75%)	13/16 (81.3%)	0.69 (0.09, 5.29)	0.723
Beta-blocker user	8 (26.7%)	3 (23.1%)	5 (29.4%)	0.83 (0.3, 2.25)	1.000
Diuretic user	7 (23.3%)	3 (23.1%)	4 (23.5%)	0.99 (0.37, 2.61)	1.000
Readmission in 30 days	9 (30%)	3 (100%)	6 (35.3%)	0.7 (0.25, 1.96)	0.691

UGIB, upper gastrointestinal tract bleeding; Values presented as frequency (%); Means and Odds ratio (95%CI); *P*-value corresponds to Logistic regression analysis.

renal impairment, as well as with the MV E/A ratio and the diastolic dysfunction (Table 3).

Discussion

In this prospective analytic study, we evaluated the usefulness of serial measurements of NT-proBNP in cirrhotic patients who were admitted with sepsis. Overall, 13 patients (43.3%) died within 30 days after admission, an infection being the most common cause of dead (92.3%). This finding was different from some previous reports from developed countries where the infection itself accounted for about 30-40% of all deaths in cirrhotic patients admitted with an infection, with

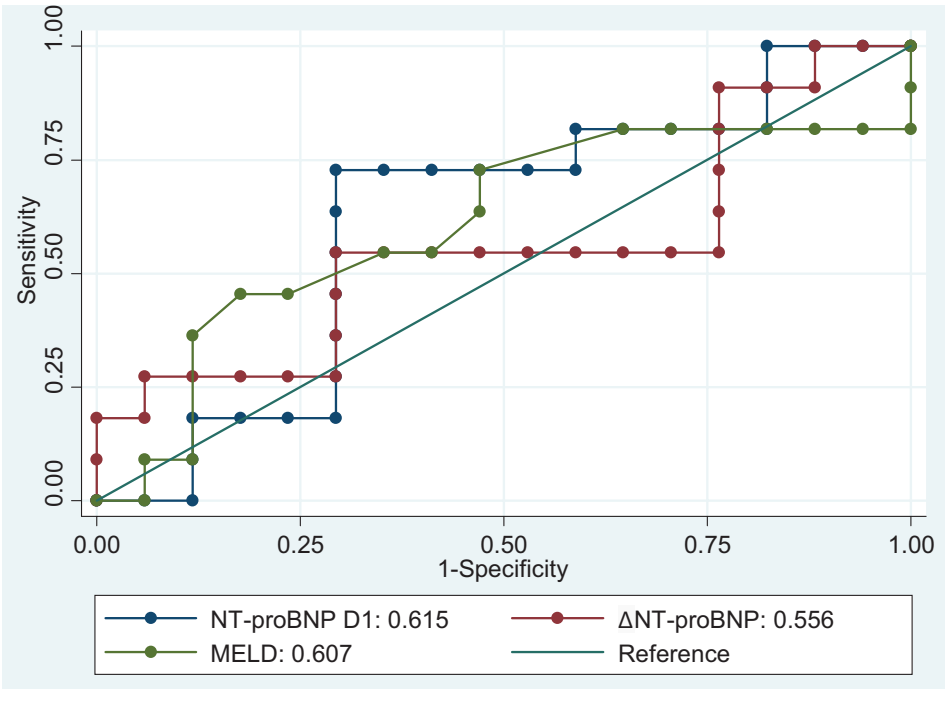

Figure 1. ROC curve for determination of NT-proBNP D1, ΔNT-proBNP and MELD score representation between sensitivity and 1-specificity.

Table 2. Factors associated with liver-related complications after admission.

Variable	No morbidity (n=17)	With morbidity (n=13)	*p*-value
NT-proBNP (pg/mL)			
D1	1266.94 ± 2136.12	4161.92 ± 4148.37	0.019*
D5	786.12 ± 1659.76	3036.09 ± 3375.07	0.026*
Δ (D5-D1)	-480.82 ± 1489.01	-587 ± 3613.25	0.914
MELD	18 ± 7	26 ± 7	0.003*
Cr (mg/dL)	1.07 ± 0.48	1.55 ± 0.69	0.031*
EKG (n=28)			
QTc ($ms^{1/2}$)	477.06 ± 57.29	498.33 ± 53.02	0.325
Echocardiography (n=24)			
E/e' ratio	9.53 ± 2.53	11.3 ± 5.51	0.410
MV E/A ratio	1.19 ± 0.38	0.85 ± 0.27	0.019*
LVEF (%)	69.13 ± 5.38	75.28 ± 3.63	0.008*
Diastolic dysfunction	11 (64.7%)	8 (61.5%)	0.130

Values presented as mean±SD; *P*-value corresponds to t-test; Liver-related morbidities HE, SBP, HRS and variceal bleeding.

Table 3. Correlation between NT-proBNP levels and clinical, laboratory and echocardiographic parameters in cirrhotic patients with sepsis.

	NT-proBNP D1		NT-proBNP D5	
	r	*p*-value	*r*	*p*-value
Diuretic user	-0.114	0.549	-0.209	0.285
Beta-blocker users	-0.139	0.463	-0.157	0.426
MELD	0.437	0.016*	0.656	<0.001*
Cr (mg/dL)	0.609	<0.001*	0.642	<0.001*
WBC ($x10^9$/L)	0.180	0.342	0.120	0.544
EKG (n=28)				
QTc ($ms^{1/2}$)	0.442	0.019*	0.478	0.014*
Prolong QTc	0.248	0.203	0.202	0.323
Echocardiography (n=24)				
E/e' ratio	0.368	0.077	0.399	0.054
MV E/A ratio	-0.528	0.008*	-0.643	0.001*
LVEF (%)	0.238	0.262	0.210	0.324
Diastolic dysfunction	0.319	0.129	0.497	0.014*

P-value corresponds to Spearman's rho correlation.

renal failure being the next common cause. This difference could partly be related to our more severe clinical setting including more critically ill patients and delayed admission due to limited resources and facilities as well as more virulent and resistant pathogens and poorer general medical care and infectious disease control compared with the developed countries.

Our data showed that NT-proBNP in the first day of admission, in day 5-after admission and the difference between the 2 measurements were not associated with the 30-day mortality. However, the role of NT-proBNP in this setting was still inconclusive due mainly to small our sample size, as even the baseline MELD score failed to show any significant association with mortality. In addition, echocardiographic parameters also showed no correlation with the 30-day mortality. Notably, 6 out of 30 patients did not undergo echocardiography for some reasons (5 in the non-survival group, 1 in the survival group).

From demographic data, only morbidity after admission, including HE, SBP, hospital acquired pneumonia and septic shock was associated with a 30-day mortality. This finding was consistent with previous studies which showed that the occurrence of hepatic decompensation or second infection markedly increased mortality in hospitalized cirrhotic patients[25].

We analyzed MELD score, NT-proBNP (D1, D5 and Δ), Cr, QTc and echocardiographic parameters for morbidity prediction. We found that NT-proBNP D1, NT-proBNP D5, creatinine and echocardiographic parameters (LVEF and MV E/A) correlated with liver-related morbidity after admission. This association could be partly examined. First, we observed that MELD score, which reflects the severity of liver disease, correlated with liver-related morbidity. Patients with more advanced liver disease were more likely to develop liver decompensation after infection. Second, renal failure exerted a greater impact on morbidity and mortality in cirrhotic patients than the other organ failures[24]. Third, cirrhotic cardiomyopathy (a chronic cardiac dysfunction occurring in cirrhotic patients and characterized by blunted contractile responsiveness to stress and by altered diastolic relaxation with electrophysiological abnormalities such as prolongation of the QT interval) occurred in the absence of any other cardiac disease[27]. We thus hypothesized that cirrhotic cardiomyopathy might play a role in the course of liver cirrhosis with sepsis, as suboptimal cardiac response could contribute to an increased risk of developing circulatory failure and HRS in cirrhotic patients under stressful conditions[20,21]. However, in our study, this concept could not be entirely proven, to small sample size and alterations of cardiac parameters during sepsis.

As mentioned previously, only LVEF and MV E/A were significantly correlated with liver-related mor-

bidity. MV E/A along with E/e' determine the diastolic dysfunction, but from our data diastolic dysfunction appeared to bear no correlation with any morbidity. The reasons for this issue could be because most of our patients had diastolic dysfunction (79.2%) and nearly all our missing data pertained to the non-survival group. Our data, however, was consistent with previous studies showing that E/A ratio ≤1 was a predictor of hepatic decompensation and death[28]. Some authors have suggested that its presence in cases of cirrhotic cardiomyopathy with the echocardiography finding of a pathological mitral E/A ratio may be sufficient for diagnosis[29]. LVEF reflects the systolic function. In normal populations, a lower LVEF usually denotes a poor outcome. In our study, all patients had a good LVEF (>60%) at baseline, and there was no difference in term of mortality, but there was a significant correlation between LVEF and liver-related morbidities, as the patients who developed liver-related morbidities had a higher LVEF. This may be due to hyperdynamic circulation from both systemic vasodilation in liver cirrhosis and sepsis resulting in increased heart rate (HR), increased cardiac output (CO), increased LVEF and decreaseed systemic vascular resistance (SVR)[5,30]. A higher LVEF, therefore, reflects a more severe hyperdynamic state and a more advanced liver dysfunction.

Bernardi M *et al.* reported that QTc prolongation was found in approximately 50% of cirrhotic patients and was shown to be significantly related to the severity of liver disease and the presence of portal hypertension[31,32]. Our data showed that incidence of QTc prolongation was 81.2%, QTc prolongation did not correlate with liver-related morbidities. Donald et al. reported that QTc was significantly in prolonged septic mice[33], which Nogueira et al. also reported that QTc was elevated among patients with sepsis[34]. Such finding were in keeping with ours showing a higher incidence of QTc prolongation in our patients than in previous studies in cirrhotic subjects without sepsis.

An important finding in our study that could be clinically relevant was that NT-proBNP significantly correlated with liver-related morbidities. NT-proBNP is secreted from the cardiac ventricles when myocardiocytes were stretched. NT-proBNP, BNP and its pro-hormone, proBNP, are sensitive markers of even mild myocardial injury, and have been found elevated in both compensated and decompensated cirrhosis[18-21]. These peptides seem to correlate with the severity of cirrhosis, the degree of cardiac dysfunction as well as myocardial hypertrophy[20]. An event of sepsis thus, leads to an ever greater cardiac dysfunction from inflammatory cytokines[4,5]. Taken together, both conditions can lead to a more severe cardiovascular dysfunction, and NT-proBNP may be helpful for early detection of cirrhotic patients with sepsis who are at a higher risk of developing liver-related morbidities. In fact, in our study NT-proBNP levels correlated not only to the cardiac index, but also to the liver and kidney functions, similar to the findings from a previous study[21]. These factors are independent risk factors in cirrhotic patents and also in the sepsis setting[22,27-32]. Therefore, if these factors correlate with NT-proBNP, it is possible that they can be a sensitive marker to predict liver-related morbidities. Larger trials are still needed to verify this possible relationship of NT-proBNP levels and the prognosis of cirrhotic patients with sepsis.

The main limitations of our study are the relatively small number of subjects and the unavoidable clinical heterogeneity of cirrhotic patients in the sepsis setting. The echocardiography data in 6 patients (5 in the on-survival group) were missing, which could account for data discrepancy in terms of mortality. The methodology we used for diagnosing diastolic dysfunction was based on the ASE/EAE Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography 2009, which was recommended by the cardiology society, and which was not the specific criteria for the diagnosis of cirrhosis cardiomyopathy as proposed at the 2005 World congress of Gastroenterology in Montreal[35]. Both of these standard criteria have not been clearly validated in cirrhotic patients with sepsis. Our data of patients with diagnosed diastolic dysfunction might not be as consistent as in previous studies. Lastly, NT-proBNP can be altered by several confounding factors such as sodium intake before admission, intravenous fluid resuscitation and concurrent alcohol consumption, we tried to limit them.

CONCLUSION

Plasma NT-proBNP level does not predict in-hospital mortality in cirrhotic patients with sepsis. However, higher plasma NT-proBNP level was associated with the development of liver-related morbidities, suggesting that it may be a potentially useful marker for prediction and early detection of complications in cirrhotic patients with sepsis.

REFERENCES

1. Bunchorntavakul C, Chavalitdhamrong D. Bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. World J Hepatol 2012;4:158-68.
2. Bonnel AR, Bunchorntavakul C, Reddy KR. Immune dysfunction and infections in patients with cirrhosis. Clin Gastroenterol Hepatol 2011;9:727-38.
3. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis 2008;28:26-42.
4. Wong F, Bernardi M, Balk R, *et al.* Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. Gut 2005;54:718-25.
5. Gustot T, Durand F, Lebrec D, *et al.* Severe sepsis in cirrhosis. Hepatology 2009;50:2022-33.
6. Sudoh T, Maekawa K, Kojima M, *et al.* Cloning and sequence analysis of cDNA encoding a precursor for human brain natriuretic peptide. Biochem Biophys Res Commun 1989;159: 1427-34.
7. Paul M, John C. B-Type natriuretic peptide as a biomarker beyond heart failure: speculations and opportunities. Mayo Clinic Proceedings 2005;80:1029-36.
8. Mukoyama M, Nakao K, Saito Y, *et al.* Human brain natriuretic peptide, a novel cardiac hormone. Lancet 1990;335:801-2.
9. Cheung BMY, Kumana CR. Natriuretic peptides-relevance in cardiac disease. JAMA 1998;280:1983-4.
10. Ljubičić N, Duvnjak M, Rotkvić I, *et al.* Influence of the degree of liver failure on portal blood flow in patients with liver cirrhosis. Scand J Gastroenterol 1990;25:395-400.
11. Gottlieb S, Kukin ML, Ahern D, *et al.* Prognostic importance of atrial natriuretic peptide in patients with chronic heart failure. J Am Coll Cardiol 1989;13:153-9.
12. Hall C, Rouleau JL, Moyè L, *et al.* N-terminal proatrial natriuretic factor: an independent predictor of long-term prognosis after myocardial infarction. Circulation 1994;89:1934-2.
13. Mitaka C, Nagura T, Sakanishi N, *et al.* Plasma-atrial natriuretic peptide concentrations in acute respiratory failure associated with sepsis: preliminary study. Crit Care Med 1990; 18:1201-3.
14. Wang F, Wu Y, Tang L, *et al.* Brain natriuretic peptide for prediction of mortality in patients with sepsis: a systematic review and meta-analysis. Crit Care 2012;16:R74.
15. Martina B, Guenter H, Siegfried L, *et al.* Prognostic value of plasma N-Terminal Pro-Brain natriuretic peptide in patients with severe sepsis. Circulation 2005;112:527-34.
16. James L J, Alexander M, Roderick T, *et al.* Natriuretic peptide testing for the evaluation of critically ill patients with shock in the intensive care unit: a prospective cohort study. Crit Care 2006;10:R37.
17. Roch A, Allardet SJ, Michelet P, *et al.* NH2 terminal probrain natriuretic peptide plasma level as an early marker of prognosis and cardiac dysfunction in septic shock patients. Crit Care Med 2005;33:1001-7.
18. Neven L, Marija G, Dražen Z, *et al.* New insight into the role of NT-proBNP in alcoholic liver cirrhosis as a noninvasive marker of esophageal varices. Croat Med J 2012;53:374-8.
19. Ramazan Y, Bulent Y, Melih K, *et al.* Brain natriuretic peptide and severity of disease in non-alcoholic cirrhotic patients. J Gastroenterol Hepatol 2005;20:1115-20.
20. Henriksen JH, Gøtze JP, Fuglsang S, *et al.* Increased circulating pro-brain natriuretic peptide (proBNP) and brain natriuretic peptide (BNP) in patients with cirrhosis: relation to cardiovascular dysfunction and severity of disease. Gut 2003; 52:1511-7.
21. Licata A, Corrao S, Petta S, *et al.* NT pro BNP plasma level and atrial volume are linked to the severity of liver cirrhosis. PLoS ONE 2013;8:e68364.
22. Bone RC, Balk RA, Cerra FB, *et al.* ACCP/SCCM Consensus Conference Committee. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644 -55.
23. Merli M, Lucidi C, Giannelli V, *et al.* Cirrhotic patients are at risk for health care-associated bacterial infections. Clin Gastroenterol Hepatol 2010;8:979-85.
24. Nagueh CP, Appleton TC, Gillebert, *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiography 2009;22;2:107-33.
25. Bajaj JS, O'Leary JG, Reddy KR, *et al.* Second infections independently increase mortality in hospitalized cirrhotic patients: The NACSELD experience. Hepatology 2012;56: 2328-35.
26. Moreau R, Jalan R, Gines P, *et al.* Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013; 144: 1426-37.
27. Møller S, Henriksen JH. Cirrhotic cardiomyopathy: a pathophysiological review of circulatory dysfunction in liver disease. Heart 2002;87:9-15.
28. Philippe M, Laurent S. The heart and cirrhosis. Cardiovasc Med 2015;18:20-4.
29. Torregrosa M, Aguadé S, Dos L, *et al.* Cardiac alterations in cirrhosis: reversibility after liver transplantation. J Hepatol 2005;42:68-74.
30. Antonio F, Francisco RB, Rui P, *et al.* The end-organ impairment in liver cirrhosis: appointments for critical care. Crit Care Res Pract 2012; Article ID 539412.
31. Bernardi M, Maggioli C, Dibra V, *et al.* QT interval prolongation in liver cirrhosis: innocent bystander or serious threat? Expert Rev Gastroenterol Hepatol 2012;6:57-66.
32. Bernardi M, Calandra S, Colantoni A, *et al.* Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. Hepatology 1998;27:28-34.
33. Donald BH, Tammy RO, Robert W, *et al.* Impaired heart rate regulation and depression of cardiac chronotropic and dromotropic function in polymicrobial sepsis. Shock 2015;43: 185-91.
34. Nogueira AC, Gonzaga L, Kawabata V, *et al.* Is the widening of the QTc associated with mortality in sepsis? Crit Care 2007; 11(Suppl 3): P38.
35. Møller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut 2008;57:268-78.