Positive Correlation between Degree of Liver Cirrhosis and N Terminal–Pro Brain Natriuretic Peptide (NT-pro-BNP)

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ABSTRACT

Background: *Liver cirrhosis (LC) is a chronic disease characterized by damage of liver parenchyme with wide fibrosis and nodules formation. One of LC complications is cirrhotic cardiomyopathy (CC). CC is diagnosed when there are more than one of the following signs: diastolic dysfunction (DD), systolic dysfunction (SD), enlargement of the cardiac chamber, electrophysiology dysfunction, and increasing of natriuretic peptide such as N terminal–pro brain natriuretic peptide (NT-proBNP). The aim of this study was to determine the correlation between degree of liver cirrhosis and increasing of the NT-proBNP.*

Method: *Cross sectional analytic study was performed with 72 LC patients from May 2014 to May 2015 in Sanglah General Hospital, Denpasar. Degree of liver cirrhosis was determined by child turcotte pugh (CTP) criteria and NT-proBNP was examined by electro chemiluminescence immunoassay (ECLIA) method. LC patients with other disorders which can cause the increase of NT-proBNP were excluded. Statistical analysis used was Spearman's correlation test.*

Results: *Of 72 LC patients, 79.2% were male. Patients with CTP A were 9 (12,5%), CTP B 19 (26,4%) and CTP C 44 (61,19%). Median of NT-proBNP in CTP A was 112 pg/mL, CTP B 130 pg/mL, and CTP C 315 pg/mL. There was a strong possitive correlation between degree of liver cirrhosis and NT-proBNP ($r = 0.686$; $p = 0.000$). In this study, there was also significant comparison between NT-proBNP and CTP A,B, and C ($p = 0,000$) and there was no significant relation between NT-proBNP and those cofounding variables ($p > 0.05$).*

Conclusion: *there was a strong possitive correlation between degree of LC and NT-proBNP.*

Keyword*: liver cirrhosis, child turcotte pugh, NT-proBNP*

ABSTRAK

Latar belakang: *Sirosis hati (SH) adalah penyakit hati menahun yang ditandai oleh kerusakan parenkim hati dan fibrosis luas disertai pembentukan nodul. Salah satu komplikasi dari SH adalah kardiomiopati sirosis (KS). Kriteria diagnosis KS adalah ditemukan lebih dari satu kelainan berupa disfungsi diastolik atau disfungsi sistolik, perubahan struktur ruang jantung, gangguan elektrofisiologi, dan peningkatan peptida natriuretik seperti N terminal–pro brain natriuretic peptide (NT-proBNP). Penelitian ini bertujuan untuk mengetahui korelasi antara derajat sirosis hati dengan peningkatan NT-proBNP pada pasien sirosis hati.*

Metode: *Penelitian ini merupakan studi potong lintang analitik terhadap 72 penderita SH dari Mei 2014 hingga Mei 2015 di Rumah Sakit Umum Sanglah, Denpasar. Derajat sirosis hati ditentukan dengan child turcotte pugh (CTP), dan NT-proBNP diperiksa dengan metode electro chemiluminescence immunoassay (ECLIA). Beberapa kondisi yang mempengaruhi peningkatan NT-proBNP dieksklusi. Korelasi derajat SH dan NT-proBNP dianalisis dengan uji Spearman.*

Hasil: *Dari 72 sampel, 79.2% laki-laki. 9 (12,5%) orang dengan CTP A, 19 (26,4%) orang CTP B, dan 44 (61,1%) orang CTP C. Median nilai NT-proBNP pada CTP A adalah 112 pg/mL, CTP B 130 pg/mL, dan pada CTP C 315 pg/mL. Terdapat korelasi positif kuat yang bermakna antara derajat penyakit SH dengan peningkatan NT-proBNP (r = 0,686 dan p = 0,000). Pada studi ini juga didapatkan perbedaan bermakna NT-proBNP antara kelompok CTP A, B, dan C. Pada studi ini, peningkatan NT-proBNP tidak dipengaruhi oleh variabel perancu (p > 0.05).*

Simpulan: *Terdapat korelasi positif kuat yang bermakna antara derajat SH dengan peningkatan NT-proBNP.*

Kata kunci: *sirosis hati, child turcotte pugh , NT-proBNP*

INTRODUCTION

Liver cirrhosis (LC) is a chronic disease characterized by damage of liver parenchyme with wide fibrosis and nodules formation. One of LC complications is cirrhotic cardiomyopathy (CC). The pathogenic processes of LC lead to change in cardiac structures and function. The clinical manifestations of CC such as diastolic dysfunction (DD), systolic dysfunction (SD), enlargement of the cardiac chamber, electrophysiology dysfunction, and increasing of natriuretic peptide (NT-proBNP).[1] Cardiac manifestation in cirrhotic patients remains a particular concern in clinical practice since cardiac dysfunction was associated with worse prognosis and higher risk for death.

N terminal–pro brain natriuretic peptide is an active form of BNP, composed of 76 amino acids, produced by the cardiac ventricles which is involved in the regulation of fluid volume and cardiovascular homeostasis. Elevation in plasma NT-proBNP reflect fluid overload. Plasma NT-proBNP is increased in a number of disease states including congestive heart failure, chronic renal failure, chronic obstructive pulmonary diasese, diabetes mellitus, hyperthyroid, anemia, sepsis, and liver cirrhosis. In LC patients, elevation of NT-proBNP as a mark of cardiac dysfunction related to liver cirrhosis.[2,3]

Child turcotte pugh (CTP) scoring system is the most commonly used clinical method for classifying LC. Score of the CTP reflects the damage of liver parenchyms. The damage of liver parenchyms related to blunt receptor of cardiac beta adrenergic, increase the ammount of endocanabinoid, nitrit oxide, carbon monoxide, and the stiffness of myocardium. Those conditions will cause diastolic, systolic, and electrophysiology dysfunction.[4,5] The relationship between the severity of liver disease and NT-proBNP as a mark of cardiac dysfunction is controversial. Although some studies have shown no relationship between degree of LC and NT-proBNP, other studies have shown a relationship between those conditions.[6,7,8,9] Aim of this study was to determine the correlation between degree of liver cirrhosis and increasing of the NT-proBNP in Sanglah General Hospital.

METHOD

Cross sectional analytic study was conducted in 72 patients consecutively in Sanglah General Hospital, Denpasar, between May 2014 and May 2015. The inclusion criteria were adult liver cirrhotic patients. Other disorders such as hypertension, congestive heart failure, coronary heart disease, atrial fibrilation, valvular heart disease, chronic obstructive pulmonary disease, stage III-V chronic kidney diasease , diabetes mellitus, hyperthyroid, sepsis, septic shock, and history of angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blockers (ARB), calcium antagonist, thrombocyte anti aggregation, digitalis, nitrate, and statin more than 1 week were excluded.

Degree of liver cirrhosis was determined by CTP criteria and NT-proBNP was examined by electro chemiluminescence immunoassay (ECLIA) method. Correlation between degree of liver cirrhosis and NT-proBNP was analyzed by using Spearman's correlation test. The comparison of NT-proBNP level between CTP groups was analyzed by Kruskall-Wallis test and continued with post hoc Mann-Whitney test to compare the increase of NT-proBNP in each CTP groups. Multivariate analysis of the cofounding variables using

Chi-square comparison test. Data which had been included in the research form, was processed by SPSS program version 21. The study was commenced after having an ethical approval by the Ethical Committee at Faculty of Medicine, University of Udayana.

RESULTS

Between May 2014 and May 2015, 72 LC patients were conducted. 79,2% were male. Mean age of patients was 47,4 ± 7,1 years. Bassed on degree of liver cirrhosis, the comparison between CTP A, B, and C were 9 (12,5%) : 19 (26,4%) : 44 (61,19%). Most of the patients came to the hospital in severe condition (CTP C). Median of NT-proBNP in CTP A was 112 (5-180) pg/mL, CTP B 130 (11,7-860) pg/mL, and CTP C 315 (86-1980) pg/mL. The lowest level of NT-proBNP was 5 pg/mL found in CTP A and the highest one was 1980 pg/mL in CTP C. Anemia and other conditions such as diuretics and beta blockers usage as a cofounding variables in this trial were found mostly in CTP C group.

Descriptive study such as frequency, mean, standard deviation, median, minimal and maximal data were used to describe the profile of LC patients in Sanglah Hospital. In this study, the number of liver cirrhosis patient in Sanglah Hospital was still high and most of them were male and came to the hospital in severe condition (CTP C). The highest median level of NT-proBNP was found in CTP C group and the cofounding variable such as anemia, diuretics, and beta blockers usage were found mostly in CTP C group.

There was a strong possitive correlation between degree of liver cirrhosis and NT-pro BNP (r = 0.686; p = 0.000). Spearman's correlation test was performed to evaluate the correlation between degree of liver cirrhosis and NT-proBNP.

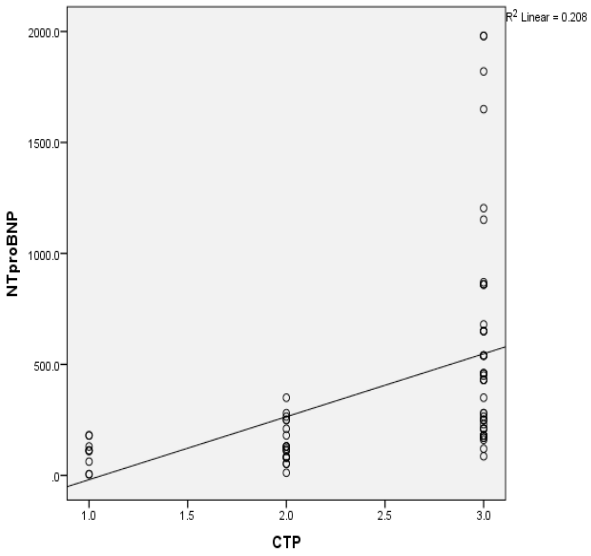

Figure 1. Correlation between degree of liver cirrhosis and NT-proBNP

There was also a significant comparison between NT-proBNP and CTP A,B, and C (p = 0,000) Table 3 shows the comparison of NT-proBNP level between each group of CTP. In this trial there was significant comparison between the group of CTP A and C, CTP B and C (p < 0.05). Kruskall-Wallis test was performed to analyze the NT-proBNP level between CTP A, B, and C. To find out the between each group of CTP we used post hoc Mann-Whitney test. Multivariate analysis of the cofounding variables such as age, sex, anemia, diuretics, and beta blockers showed there were no significant relation between NT-proBNP and those variables (Table 4). Multivariate analysis using Chi-square comparison test.

Table 1. Baseline characteristics of the patients

Variables	Total n (%)	CTP A n (%)	CTP B n (%)	CTP C n (%)
Patients (n)	72	9 (12.5%)	19 (26.4%)	44 (61.1%)
Sex				
Male	57 (79.2 %)	8 (88.9%)	12 (63.2%)	37 (84.1%)
Female	15 (20.8%)	1 (11.1%)	7 (36.8%)	7(15.9%)
Age (year)	47.4 ± 7.1	45.67 ± 7.8	46.63 ± 8.1	48.69 ± 6.4
NT-proBNP (pg/mL)	210 (5-1980)	112 (5-180)	130 (11,7-860)	315 (86-1980)
Anemia	43 (59%)	3 (33%)	8 (42.1%)	32 (72.7%)
Drugs				
Diuretics	32 (44.4%)	0 (0%)	9 (47.4%)	23 (52.3%)
Beta blockers	35 (48.6%)	0 (0%)	11 (57.9%)	24 (54.5%)

NT-proBNP: N terminal-pro brain natriuretic peptide; CTP: child turcotte pugh

Table 2. Correlation between degree of liver cirrhosis and NT-proBNP

Variable	Total	CTP A	CTP B	CTP C	r	p
NT-proBNP (pg/mL)	210 (5-1980)	112 (5-180)	130 (11,7-860)	315 (86-1980)	0,686	0,000

NT-proBNP: N terminal-pro brain natriuretic peptide; CTP: child turcotte pugh

Table 3. The comparison of NT-proBNP level between each CTP groups

Group	p
CTP A and CTP B	0,182
CTP A and CTP C	0,000
CTP B and CTP C	0,000

CTP: child turcotte pugh

Table 4. Multivariate variables that were influenced NT-proBNP level

Variable	p
Age	0,96
Sex	0,28
Anemia	0,19
Diuretics	0,41
Beta Blockers	0,48

DISCUSSION

Incidence for LC was still high. In our study, there were 72 patients with LC, 79.2% were male, the youngest age was 30 years and the oldest was 60 years, mean of age was 47.40 ± 7.1 years. Based on the degree, CTP C was the most of all (61.1%). Results from our study was similar to studies from Indrawan et al that stated that 72.7% of 72 LC patients at Sanglah Hospital in 2014 were male.[10] Suwindnya et al also stated that among LC subjects, the youngest age was 25,4 years and the oldest was 69.10 years, with mean age was 50,86 ± 9,84 years.[11] LC are often assymptomatic at early state due to parenchymal compensation providing normal liver function, causing a delayed arrival at health care provider. As the disease progressing, compensation is no longer adequate and liver failure along with portal hypertension emerged.

LC complications occur along with the severity of the liver disorder. Cirrhotic cardiomyopathy is one of the complication, which based on gastroenterology world congress in Montreal in 2005 is diagnosed by more than one finding: diastolic dysfunction (DD) or systolic dysfunction (SD) on LC, hearth chamber structure changing (enlargement of the atrium), electrophysiological disorder (prolongation of QT interval), and elevation of natriuretic peptide such as NT-proBNP.[12] In this study, we searched for correlation of NT-proBNP and the severity of LC. Median of NT-proBNP values on CTP A : B : C were 112 (5-180) pg/mL **:** 130 (11.7-860) pg/mL **:** 315 (86-1980) pg/mL. NT-proBNP elevated along with the severity of liver damage with the highest median of NT-proBNP was in the CTP C group. The results were consistent with Eldeeb et al who found a significant elevation of NT-proBNP on CTP C which correlated to enlargement of left atrium, and Papasterigiou et al got NT-proBNP elevation was more in CTP C subjects which associated with more DD incidence on CTP C.[4,6]

We found a strong positive correlation between severity of LC and NT-proBNP ($r = 0.686$; $p = 0.000$). Liver parenchymal damage caused blunted of beta receptors responses on the heart muscles, increasing of endocanabinoids, nitric oxide (NO), carbon monoxide (CO), and the myocardial wall stiffness that led to systolic, diastolic, and electrophysiological disorder in LC.[13] CTP score reflects the severity of liver parenchymal damage, so the more severe the LC caused more severe heart disorder in LC. NT-proBNP elevated in heart disorders such as congestive heart failure and other conditions like cirrhotic cardiomyopathy.

LC severity correlated with LC related-heart disorder, and the heart disorder correlated with NT-proBNP elevation. On LC, there are systolic and diastolic dysfunctions that causes volume and pressure overload, that increases NT-proBNP secretion. Diastolic dysfunction appears on the early stage of cirrhotic cardiomyopathy, followed by systolic dysfunction on the late stage that gives the heart failure symptoms.[14] Some studies supported our results are Ziada et al and Eldeeb et al with moderate correlation ($r = 0.485$; $p = 0.019$; and $r = 0.4$; $p = 0.0001$) and Henriksen et al with strong correlation ($r = 0.89$; $p < 0.001$).[6,7,15]

Based on LC severity, in our study there was a significant difference for NT-proBNP in CTP A, B, and C. We also conducted post hoc analysis to find the difference of NT-proBNP values in each CTP groups, we found significant differences between CTA A and C groups, and between CTP B and C ($p < 0.05$). At the early stage of LC, heart disorder occured as diastolic dysfunction that could elevated NT-proBNP, that may caused no NT-proBNP value differences between CTP A dan B in our study. NT-proBNP elevated more in CTP C due to more severe the heart disorder occured in CTP C.[13,14] It explained our results where there were significant differences of NT-proBNP between CTP A and C, and between CTP B and C.

We analyzed some cofounding variables, which were anemia, beta blockers, and diuretics usage, and there were no significant correlations between those variables and NT-proBNP elevations. NT-proBNP was not affected by anemia, beta blockers and diuretics usage in this study. On severe LC with severe complications, diuretics and beta blockers were required and so in our study, incident of anemia, beta blockers, and diuretics usage were more in CTP C.

CONCLUSION

There was strong positive correlation between degree of LC and NT-proBNP.

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