The Correlation of the Hepcidin Ferritin Ratio and the Severity of Liver Cirrhosis

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Abstract: **Background.** Hepcidin serum level was influenced by the inflammation and iron deposit in *chronic liver disease / CLD*), but the correlation between the hepcidin ferritin ratio and the severity of liver cirrhosis was still not clear. The aim of this study was to found correlation between the hepcidin ferritin ratio and the severity of liver cirrhosis. **Methods.** The study was conducted in Gastroenterohepatology Division, Internal Medicine Department, Faculty of Medicine, University of Sumatera Utara. The study was an analytic comparative, cross sectional study. The subject were liver cirrhosis patients that fulllfiled inclusion criteria and informed consent. **Results.** From 78 liver cirrhosis patients, mean age was 51.36 ± 12.6 years old. Male was more than female (44 (56%), 34 (43.6%), respectively. We found that there was no significant difference of the hepcidin ferritin ratio among Child pugh A , Child pugh B and Child pugh C patients (0.17 ; 0.11 and 0.28, respectively, with p = 0.161). **Conclusion.** There was no significant difference of the hepcidin ferritin ratio among severity of liver cirrhosis.

1 INTRODUCTION

Hepcidin is the hormone of iron which produced in the liver as a response to inflammation and iron that triggered by cytokines during inflammation. Hepcidine inhibits iron entry into the compartment of plasma, as the principal regulator of systemic iron homeostasis (Piperno, 2009). It is produced almost exclusively by the hepatocytes as response to the iron (Pigeon, 2001) and stimuli of inflammation (Nicolas, 2002). When the level of iron is deficient, hepatocytes will develop less or no hepcidin, and allowing more iron to enter into plasma (Ramos, 2011).

Iron is an essential element and required in metabolic processes such as, oxygen transport, DNA synthesis and energy production. The excess of iron can be harmful, in part through the formation of reaxtive oxygen species (ROS), and it is potentially lethal (Hentze, 2004). The correlation between expression of hepcidin and iron burden or inflamation condition has been reported. The concentration of hepcidin is affected by inflammation and iron stores in the condition of chronic liver disease (CLD), but less is known about the correlation between the ratio of hepcidin : ferritin and the severity of liver cirrhosis.

Liver cirrhosis is a liver disease complication which characterized by the disapperance of liver cells and the formation of connective tissue in an irreversible liver (Dooley, 2011).

The study was conducted to evaluated level of hepcidin, ferritin and the hepcidin:ferritin ratio by cross sectional study in consecutive patients with liver chirrosis. The purpose of this study was to determine the serum levels of hepcidin ferritin ratio and to evaluate its correlation to the severity of liver chirrosis.

2 METHOD

This was an analytic comparative, cross-sectional study on liver chirrosis patients, that were admitted to Gastroenterohepatology Division, Internal Medicine Department, Faculty of Medicine, University of Sumatera Utara.

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2.1 Patients Selection

Serum hepcidin and ferritin was measured in 78 liver cirrhosis patients that fulllfiled inclusion criteria and informed consent. The inclusion criteria was liver cirrhosis patients that confirmed by clinical findings, laboratory parameters, imaging or histopathological examination.

The exclusion criteria were hepatoma, sepsis and chronic kidney disease and refused to participated in the study.

2.2 Hepcidin: Ferritin Ratio

2.2.1 Hepcidin

The blood samples were collected from cubital vein samples in the morning after 12 hours of fasting.The determination of hepcidin hormone concentration in the serum was used ELISA method . It is under the following reference ranges: women - from 57.5 to 123 ng / ml; males - 88.7 to 135 ng / ml.

2.2.2 Ferritin

The blood samples were obtained by vein puncture. The measurement of ferritin used Roche Elecsys-170 method which a sandwich principle with a total duration time of 18 minutes. The concentration of iron serum (women: 10.5 to 23 mmol / L ; men: 12.5 to 26 mmol / L;), total iron-binding capacity (JAC, 44 to 66 mmol / L), and serum ferritin (females: 10 to 140 mg / L men: 20 to 280 mg / L). It was determinated and the saturation of transferrin (with reference range 20-40%).

2.3 Statistical Method

The data was analyzed by univariate analysis using the SPSS 22nd version

3 RESULTS

The study was investigated 78 patients that classified in inclusion criteria. There were 78 patients with liver chirrosis, male patients (56,4%) were dominant than female patients (43,6%). The average age of the patient was 52nd years. Liver chirrosis patients with ascites are 63 persons (80,8%). The severity of liver cirrhosis is divided accroding to the Child Pugh category. The number of patient that included in the Child Pugh A was 15 persons (19,2%), Child Pugh B was 17 persons (21,8%) and Child Pugh C was 46 persons (59%). The severity of liver cirrhosis based on the Child Pugh category will be compared to its hepcidin ferritin ratio. Characteristic of research subjects can be seen in Table 1.

Table 1 : Characteristic of Patients

Variable	n = 78
Gender	
Male	44 (56,4%) [a]
Female	34 (43,6%)
Age	51,36± 12,6 [b]
Ascites	
Yes	63 (80,8%) [a]
No	15 (19,2%)
Hepatic Encephalopathy	
Yes	9 (12,5%) [a]
No	69 (87,5%)
Child Pugh	
A	15 (19,2%) [a]
B	17 (21,8%)
C	46 (59%)
HFR Category	
≥ 0,1	34 (43,6%) [a]
< 0,1	44 (56,4%)

[a] Categorical data : n(%)
[b] Numeric data, normal distribution : mean ± SD

From laboratory data, the average of the serum iron was 36 mmol/L, the average of the ferritin was 237 mg/L and the average of hepcidin was 17,74 ng/mL. The laboratory characteristic of research subjects can be seen in Table 2.

Table 2 : Laboratory characteristics of research subjects

Baseline characteristics	Value
Hemoglobin (gr/dL)	10,15 ± 2,53[a]
Platelet count (thousand/mm^3)	144.500 (12.000-654.000)[b]
Albumin (g/dL)	2,3 (0,9-3,7)[b]
INR	1,28(0,89-3,71)[b]
Total Bilirubin (mg/dL)	2,4 (0,2-21,9)[b]
AST (U/L)	52 (15-377)[b]
ALT (U/L)	43 (8-246)[b]
ALP (U/L)	120,75 ± 53,41[a]
SI (ug/dL)	36 (10-345)[b]
TIBC (ug/dL)	165,5 (59-520)[b]
Ferritin (ug/dL)	237 (4,16-6078)[b]
Reticulocyte	1,9 (0,9-7,87)[b]

CRP (mg/dL)	2,6 (0,1-14)[b]
Hepcidin	17,74 (1,15-275,22)[b]
IL-6	8,22 (0,62-2107,9)[b]

[a] Numerical data, normal distribution : mean ± SD
[b] Numerical data, abnormal distribution : median (minimum-maximum)

A comparison of laboratory findings between liver cirrhosis with Child Pugh A, B and C group can be seen in Tabel 3. There was no significant difference between the hepcidin : ferritin ratio among Child pugh A , Child pugh B and Child pugh C of patients (0.17 ; 0.11 and 0.28, respectively, with p = 0.161).

Table 3 : Comparison of Laboratory Parameters Between Hepatic Cirrhosis of Child Pugh A, B, and C

Laboratory	**Child Pugh A (n =15)**	**Child Pugh B (n = 17)**	**Child Pugh C (n= 46)**	**P**
Total Bilirubin (mg/dL)[b]	0,8 (0,3 – 4,3)	1,8 (0,2 – 21,9)	3,15 (0,2 – 13,6)[#]	0,007 *
INR [b]	1,06 (0,89 – 2,1)	1,18 (0,89 – 2,26)	1,39 (0,89 – 3,71)[#]	0,008 *
Albumin (g/dL) [b]	3,2 (1,7 – 3,7)	2,3 (0,9 – 3,5)[#]	2,3 (1 – 3,6) [#]	0,001 *
Hemoglobin (g/dL)[a]	11,43 ± 2,5	10,13 ± 2,69	9,69± 2,33	
Leukocytes (cell/mm^3)[b]	8.620 (3.300 – 22.930)	5.850 (2.100 – 29.000)	6.625 (1.830 – 35.190)	0,140
Platelet count (thousand/ mm^3)[b]	268.000 (12.000 – 420.000)	164.000 (22.000 – 509.000)	127.000 (15.000 – 654.000)[#]	0,010 *
Reticulocyte [b]	1,3 (0,9 – 6,6)	1,9 (1 – 4,03)	2,05 (0,9 – 7,87)	0,057
SI (ug/dL)[b]	36 (11 – 100)	37 (12 – 160)	31,5 (10 – 345)	0,862
TIBC (ug/dL)[b]	146 (59 – 452)	195 (65 – 490)	170,5 (100 – 520)	0,356
Hepcidin [b]	34,08 (1,75 – 275,22)	30,19 (1,26 – 178,6)	9,97 (1,15 – 109,24)[#!]	0,019 *
Ferritin (ug/dL) [b]	121 (4,16 – 896)	546,55 (5,08 – 1249,5)	237 (8 – 6070)	0,310
Hepcidin:Ferritin[b]	0,17 (0,0-8,19)	0,11 (0,0-1,65)	0,28 (0,0-13,62)	0,161

*p<0.05
[#] The result in this group significantly different with the Child Pugh A group (p<0,05)
[!] The result in this group significantly different with the Child Pugh B group (p<0,05)
[a] Numerical data, normal distribution : mean ± SD
[b] Numerical data, abnormal distribution : median (min-max)

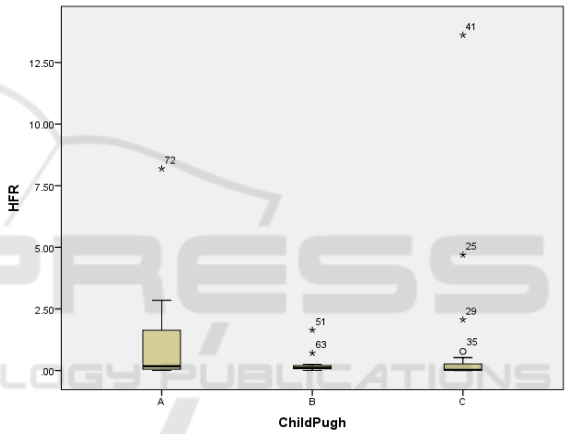

Figure 1 : Comparison of serum hepcidin ferritin ratio and the severity of liver chirrosis

4 DISCUSSION

The concentration of hepcidin serum has been evaluated in inflammatory diseases and iron-related disorders (Van Der, 2010; Oustamanolakis, 2011). There is lack of data regarding to hepcidin concentrations in the liver chirrosis. Although some study showed that hepcidin concentration could be utilized as a cirrhosis diagnostic tool, but it is remains unclear (Tsochatzis, 2010). The elevated of iron stores and inflammation may increases serum hepcidin and ferritin levels. However, hepcidin levels of liver disease patients were reduced in correlated to ferritin, resulting a decreased hepcidin:ferritin ratio (Terrence, 2012). This was confirm in our study, we found that there was significantly difference of hepcidin serum level in

Child pugh A, B and C group with $p<0.05$, but we also found that there was no significant difference of the hepcidin:ferritin ratio among Child pugh A, Child pugh B and Child pugh C patients (0.17 ; 0.11 and 0.28, respectively, with $p = 0.161$).

The data showed that there was a progressive fall in the hepcidin serum level in patient with liver cirrhosis, indicating a correlation between the presence and severity of liver cirrhosis and hepcidin concentration. The increased accumulation of iron in the body also directly related to ferritin serum level.

The study concluded that increasing hepatic fibrosis in CLD is not associated with decreased hepcidin, relative to ferritin. Further study are needed for the ratio of hepcidin:ferritin as a potential biomarker to determine the severity of liver cirrhosis.

5 CONCLUSIONS

There was no significant difference of the hepcidin ferritin ratio among severity of liver cirrhosis.

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