Serum level of IL-6 in liver cirrhosis patients

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Abstract. Cytokines are polypeptides that have a wide spectrum of inflammatory, metabolic, hematopoietic and immunologic regulatory properties. The liver represents an important site of synthesis and clearance organ for several cytokines. This study aimed to evaluate serum IL-6 in liver cirrhosis with the type of underlying disease, child pugh group and various clinical and laboratory parameter. This cross-sectional study was at Adam Malik General Hospital and Pirngadi General Hospital from July - December 2016. We examine 75 patients with liver cirrhosis. The exclusion criteria were hepatoma, sepsis and renal impairment. There were 28 (37.3%), 8 (10.6%) and 39 (52%) for HBV-positive; HCV-positive and HBV- HCV negative liver cirrhosis patients, respectively were 14 (18.7 %), 15 (20 %) and 46 (61.3%) for Child-Pugh A, B and C respectively. There was no significant difference value of IL-6 between HBV positive, HCV positive, and HBV-HCV negative group (7.7/6.1/10.9). There was no significant difference value of IL-6 between child pugh A, B, and C group (4.2/11.0/7.9).

1. Introduction

IL-6 is a cytokine that had biological activities in immune regulation, hematopoiesis, inflammation, and oncogenesis. IL-6 is a four-helical cytokine of 184 amino acids that is synthesized by fibroblasts, monocytes, macrophages, T cells and endothelial cells.[1]

Interleukin-6 was also identical with hepatocyte stimulating factor2. Under inflammatory conditions, induces the liver to synthesize a group of proteins called acute phase proteins.[2] IL-6 have an important role in liver regeneration. Only 2 hours after hepatectomy, the level of TNF alpha increased followed by a dramatic upregulation of IL-6 levels in liver vein.[3]

The cytokines play roles in hepatic inflammation in many liver disorders, resulting in fibrosis and cirrhosis.[4] Prystupa found significantly higher concentrations of interleukin-6 were demonstrated in Child class C, compared to child class A in Alcoholic liver cirrhosis.[5]We aimed to evaluate serum IL-6 in liver cirrhosis not only in alcoholic liver cirrhosis but also in another underlying disease.

2. Methods

2.1. Patient Selection

This study was a cross-sectional study design on 75consecutive liver cirrhosis patients that were admitted to General Hospital Haji Adam Malik Medan and Pirngadi General Hospital from July to December 2016.The clinical and laboratory parameter was from the subjects. Exclusion criteria were

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hepatoma, sepsis and renal impairment. The diagnosis of liver cirrhosis was on anamnesis, clinical finding, laboratory parameters and ultrasound.The local ethics committee approved this study.

2.2. Definition of Hepatitis B and C

Diagnosis of HBV and HCV viral infection based on the results of positive HBV serologic marker (HBsAg) and HCV serologic marker (Anti HCV).

2.3. Statistical Methods

We analyzed IL-6correlation with the type of underlying disease and the clinical and laboratory parameter.Data analysis was performed through univariate analyses using the SPSS 22nd version (SPSS Inc., Chicago).

3. Result

This study was 75 patients who met the inclusion criteria, divided into three groups HBV positive, HCV positive, HBV and HCV negative patients.

Table 1. Characteristic of patients.

Hepatitis	Sex (M/F)	Age	Ascites(Y/N)	Childpugh (A/B/C)
HBV (n=28)	(20/8)	53±12.5	(24/4)	(5/7/16)
HCV (n=8)	(4/4)	53±12.5	(7/1)	(1/1/6)
None (n=39)	(20/19)	51±13.3	(30/9)	(8/7/24)

Table 1 showed the mean age of HBV, HCV, None HBV-HCV groups were53±12.5; 53±12.5; 51±13.3y.o, respectively.

Table 2. Laboratory parameter of patients based on underlying disease.

Hepatitis	IL-6	INR	Albumin	CRP	Platelet (10^3)	Ferritin	ALT	AST
HBV	7.7	1.3	2.5	2.1	129	313.5	49	49
(n=28)	(0.9-76.2)	(0.9-2.1)	(1.6-3.5)	(0.2-7.8)	(22-487)	(4.2-6078)	(10-226)	(20-124)
HCV	6.1	1.5	2.4	2.4	156.5	116.8	29	40.5
(n=8)	(0.95-20.04)	(0.94-2.1)	(1.9-3.6)	(0.1-6.0)	(41-315)	(8.3-990)	(8-75)	(18-196)
None	10.9	1.2	2.2	2.6	168	240	43	60
(n=39)	(0.62-133.75)	(0.9-3.7)	(0.9-3.7)	(0.5-8.4)	(15-654)	(8-2887)	(11-246)	(15-377)

Table 2 showed there was no significant difference between each group for all laboratory parameters (p>0.05).

Table 3. Laboratory parameter of patients based on Child pugh group.

Childpugh	IL-6	CRP	Ferritin	AST	ALT
A(n=14)	4.2 (1.8-133.8)	2.1 (0.5-6.4)	144.5 (4.2-896.0)	71.5 (19.0-134.0)	60 (10-226)
B(n=15)	11.0 (0.6-58.1)	2.6 (0.2-7.4)	393 (5.1-1249.5)	48 (15-242)	48 (10-75)
C(n=46)	7.9 (0.6-85.2)	2.45 (0.1-8.4)	240 (8-6078)	52 (18-377	41 (8-246)

Table 3 showed there was no significant difference between child pugh group for IL-6, CRP, Ferritin, AST and ALT (p>0.05).

Table 4. Correlation between laboratory parameters and IL-6/CRP.

	IL-6	CRP
Ferritin	0.15	0.16
INR	0.13	0.17

Albumin	-0.363[a]	-0.18
Hb	0.11	-0.72
Leu	0.44[a]	0.05
Platelets	0.30[a]	-0.44[a]
CRP	0.19	-
ALT	-0.24	0.20
AST	0.02	0.35[a]
GGT	0.11	0.05

[a]p<0.01

Table 4 showed a correlation of IL-6 and CRP with laboratory parameters. There were significant weak positive correlations for Leukocyte (r=0.44) and Platelets (r=0.30) with IL-6 (p<0.01). There was a significant weak negative correlation between Albumin (r=-0.363) and IL-6 (p<0.01). For CRP, there were significant weak positive correlations and moderate negative correlation (p<0.01) with AST and platelets (r=0.35, r=-0.44, respectively).

Table 5. Multivariate analysis of laboratory parameter and IL-6.

	Coefficient	p-value
Albumin	-0.06	0.588
Platelets	0.148	0.233
Leukocyte	0.36	0.007

Table 5showed multivariate analysis of IL-6 with albumin, platelets, and leukocyte. Leukocyte has a significant positive correlation with IL-6.

Table 6. Multivariate analysis of laboratory parameter and CRP.

	Coefficient	the
AST	0.3	0.009
Platelets	-0.001	0.993

Table 6 showed multivariate analysis of CRP with AST and platelets. AST has a significant positive correlation with CRP.

4. Discussion

This study found that there was a significant positive correlation between Leucocyte and Platelets with IL-6. There was a considerable negative correlation between Albumin and IL-6 (p<0.01).

Tilget al found that parameters of liver injury (AST, bilirubin), hepatic synthesis function (albumin, INR), leukocyte and platelets and Ferritin were correlated with IL-6.[6]

This study found no significant differences between HBV, HCV and HBV HCV negative group with IL-6. Tanget et al showed that HBV affected serum IL-6 levels.[7] Galun et al found. Conversely, IL-6 can also mediate HBV entry into hepatocytes. IL-6 facilitates HBV infection *in vitro* and *in vivo.*[8] Al-Tamimi noticed there was a significant positive correlation between HCV infection and IL-6.[9] The other studies above examined only each underlying disease such as HBV positive or HCV positive, but in our study, we compared between HBV positive, HCV positive and HBV HCV negative in liver cirrhosis.

This study found no significant differences between HBV, HCV and HBV HCV negative group with CRP. Al-Tamimi found there was no significant difference between HCV infection and CRP levels.[9]

Prystupa et al found that the concentrations of IL-6 in the group with classes A, B, and C liver cirrhosis were significantly higher than those in the control group. Moreover, substantially higher IL-6 concentrations were observed in the group with classes B and C liver cirrhosis, as compared to the

group of alcoholicswithoutcirrhosis. Higher IL-6 concentrations were also found in the group with class C liver cirrhosis in comparison with the group with class A cirrhosis.[5] Genesca et al found that only interleukin-6 levels had significant correlations with Child score, plasma renin activity, serum and urinary sodium, and mean arterial pressure.[10]Goral found a positive correlation between serum inflammatory cytokine levels (TNF-alpha, IL-1beta, IL-2R, IL-6, IL-8) and the severity of liver cirrhosis.[11] Saragih and Ratnasari found that raising of IL-6 levels is followed with increasing of Child-Pugh Score modification, but this correlation is weak and not statistically significant.[12] This study found that there was no significant difference between child pugh group for IL-6, CRP, Ferritin, AST and ALT maybe because in our study we included not only one underlying disease, which each of them may have an impact to IL-6 levels and just 13% subjects had hepatic encephalopathy.

5. Conclusion

This study found no significant differences between underlying disease of cirrhosis patients and child pugh group to IL-6 level.

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