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Association Between Serum IL-6, IL-10, IL-12, and IL-23 Levels and Severity of Liver Cirrhosis

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ABSTRACT

Background: Liver cirrhosis contributes to high liver-related mortality globally. Systemic inflammation mediated by immune cells contributes to the progression of liver cirrhosis. Growing evidence shows that several pro- and anti-inflammatory cytokines might have an important role in liver cirrhosis. **Objective:** To evaluate the association between serum IL-6, IL-10, IL-12, and IL-23 levels and severity of liver cirrhosis. **Methods:** This observational study was carried out at the Department of Internal Medicine, Universitas Sumatera Utara, Indonesia from March 2018 to August 2019. The severity of liver cirrhosis was assessed by using the Child-Pugh score. IL-6, IL-10, IL-12, and IL-23 levels, hepatitis and renal function were measured in all study subjects. Independent t-test and Mann-Whitney tests were conducted to observe differences between groups. **Results:** A total of 78 liver cirrhosis patients were enrolled, mean age was 50.6±11.4. Median serum IL-6, IL-10, IL-12, and IL-23 levels were 24.5(2.6-46.4)pg/ml, 2.1(0.4-9.3)pg/ml, 3.5(1.4-20.8)pg/ml and 20.3(9.2-218) pg/ml, respectively. A higher IL-6 level was associated with more severe liver cirrhosis (p=0.001) and the presence of hepatic encephalopathy (p=0.018). Higher IL-23 level was found in patients with no hepatic encephalopathy (p=0.049). There was no association between serum cytokines levels and hepatitis viral infection status. **Conclusion:** IL-6 is associated with the severity of liver cirrhosis.

Keywords: Cytokines, interleukin 6, liver cirrhosis, hepatic encephalopathy.

1. BACKGROUND

Liver cirrhosis is the 11th cause of death worldwide (1). It is a high-burden disease with approximately one million deaths in 2010 (2). In Indonesia, the high prevalence of hepatitis virus infection contributes to the increasing number of liver cirrhosis incidence (3). Several mechanisms can cause liver injury that triggers necroinflammation, fibrogenesis and diffuse nodular regeneration, leading to liver cirrhosis (4). Cirrhosis patients often exhibit systemic inflammation. The activation of innate and adaptive immune cells results in an increased production of pro-inflammatory cytokines (5). The inflammation is a complex process by which the liver responds to local insults, attempting to restore the original structure and liver function. The inflammation induces gradual replacement by non-functional fibrotic scar. The imbalance between immense fibrosis versus liver tissue regeneration gives rise to liver cirrhosis (6). Accumulating evidence showed that hepatic and systemic injury is related to the high production of pro-inflammatory cytokines (6). On the other hand, studies reported that hepatitis viral infections mainly by hepatitis B virus and/or hepatitis C virus are the major causes of cirrhosis (7). Some of the cytokines have been reported to be involved in the development of hepatitis viral infection leading to chronic liver disease (8). IL-6, IL-8, IL-10 and IL-23 are involved with HBV infection (9, 10), while IL-10 and IL-12 predominant responses are associated with progression of HCV infection (11, 12).

2. OBJECTIVE

This study aimed to evaluate the association between serum IL-6, IL-10, IL-12, and IL-23 levels and the severity of liver cirrhosis.

3. MATERIALS AND METHODS

This observational study was conducted in the Department of Internal Medicine, Universitas Sumatera Utara, Indonesia from March 2018 to Au-

gust 2019 after approval from the institutional Ethical committee (Ref no.53/TGL/KEPK FK USU-RSUP HAM/2018).

This study included all patients aged above 18 years old with liver cirrhosis who visited Haji Adam Malik General Hospital Medan, Indonesia. The diagnosis of liver cirrhosis was based on the result of transient elastography (TE, FibroScan, Echosens, France). Result ≥12.5kPa was considered liver cirrhosis (13). Subjects with malignancy, systemic infection, and chronic kidney disease were excluded from the study.

Data on gender, age, the occurrence of viral hepatitis, severity of liver cirrhosis, the occurrence of hepatic encephalopathy and ascites, several blood parameters, and interleukins were collected. Diagnosis of viral hepatitis infection was based on the result of hepatitis B surface antigen (HbsAg, AxSYM kit HBsAg version 3.0, Abbott Laboratories) and hepatitis C antibody (Anti-HCV, AxSYM kit Anti HCV version 3.0, Abbott Laboratories) serologic test. Patients were grouped into viral and non-viral hepatitis groups. The severity of liver cirrhosis was assessed by Child-Pugh scoring, then was classified into groups A, B, and C (14). Overt hepatic encephalopathy was diagnosed clinically based on impairment mental status as defined by the West Haven Criteria (WHC) and impairment neuromotor function. It was assessed using psychometric hepatic encephalopathy score (PHES) (15). Ascites was assessed by physical examination and abdominal ultrasound.

Characteristics	n(%)
Gender	
Male	46(58.9%)
Female	32(41%)
Age, year	50.6(±11.4)[a]
Child-Pugh classification	
A	2(2.5%)
B	34(43.5%)
C	42(53.8%)
Hepatic encephalopathy	
Yes	38(48.7%)
No	40(51.2%)
Ascites	
Yes	60(76.9%)
No	18(23.1%)
Hemoglobin, g/dl	9.5(5.5-16.4)[b]
Leukocyte, cell/mm^3	6890(1029-31670)[b]
Platelet, thousand/mm^3	99.5(30.0-67.7)[b]
Creatinine, g/dl	0.79(0.26-9.51)[b]
Albumin, g/dl	2.3(1.2-4.8)[b]
INR, second	1.46(0.63-3.73)[b]
Total bilirubin level, mg/dl	2.3(0.6-9.4)[b]
IL-6, pg/ml	24.7(2.6-46.4)[b]
IL-10, pg/ml	2.1(0.4-9.3)[b]
IL-12, pg/ml	3.5(1.4-20.8)[b]
IL-23, pg/ml	20.9(9.2-218)[b]

Table 1. Subjects' characteristics. n: number; INR: international normalized ratio; aMean(±SD); bMedian(min-max)

Laboratory findings, pg/ml	Non-viral hepatitis (n = 40)	Viral hepatitis (n = 38)	p-value	Child-Pugh A+B (n = 36)	Child-Pugh C (n = 42)	p-value	Non-HE (n = 42)	HE (n = 34)	p-value
IL-6	25.6(2.6-45.6)	23.3(2.9-46.4)	0.700	14.4(2.6-45.6)	30.9(5.3-46.4)	0.001*	18.2(2.6-45.1)	32.4(5.3-46.4)	0.018*
IL-10	1.9(0.4-9.1)	2.3(0.5-9.3)	0.183	2.1(0.4-9.3)	2.1(0.7-9.1)	0.888	2.1(0.4-7.0)	2.2(0.5-9.3)	0.630
IL-12	3.5(1.5-12.8)	3.2(1.4-20.8)	0.599	3.3(1.5-20.8)	3.6(1.4-14.4)	0.748	4.0(1.5-20.8)	3.3(1.4-14.4)	0.066
IL-23	20.9(9.2-77.2)	20.3(13-218)	0.487	20.9(9.7-93.3)	20.3(9.2-218)	0.318	23.8(9.7-218)	20.3(9.2-55.4)	0.049*

Table 2. Association between cytokine levels and hepatitis viral infection status, severity of liver cirrhosis, and hepatic encephalopathy. *p<0.05; HE: hepatic encephalopathy; Median (min-max)

Statistical analysis

All data were tabulated and expressed as mean±SD or median(minimum-maximum) value. The comparison of data in different groups was analyzed with an independent t-test or Mann-Whitney test based on the Shapiro-Wilk normality test. Statistical significance was considered if p<0.05. Statistical analysis of the data was done using SPSS Software (version 22.0, SPSS Inc., Chicago).

4. RESULTS

A total of 78 subjects were enrolled in this study. Of which, 46 (58.9%) were male. The mean age of subjects was 50.6±11.4 years. Most of the patients (53.8%) were classified into class C on the Child-Pugh score. The highest serum cytokine level was observed in IL-6 (24.5 pg/ml). 38 (48.7%) subjects manifested hepatic encephalopathy and 60 (76.9%) subjects had ascites. Subjects' characteristics including the value of blood parameters was shown in Table 1.

A higher IL-6 level was associated with more severe liver cirrhosis (p=0.001). IL-6 level was associated with hepatic encephalopathy (p=0.018). Patients with hepatic encephalopathy had higher IL-6 levels. IL-23 level was lower in patients with hepatic encephalopathy (p=0.049). IL-10 and IL-12 were not associated with the severity of liver cirrhosis and hepatic encephalopathy (p>0.05). Interleukins were not associated with viral hepatitis (Table 2). The severity of liver cirrhosis was not associated with other laboratory parameters (Table 3).

5. DISCUSSION

IL-6 level was associated with liver cirrhosis severity based on Child-Pugh scoring. However, IL-10, IL-12, and IL-23 failed to show similar results. Salgüero et al. also mentioned that inflammatory cytokine IL-6 was associated with Child-Pugh score (16). Prystupa et al. also

Laboratory findings	Child Pugh A+B (n = 36)	Child Pugh C (n = 42)	p-value
Age, year[a]	52.0(±10.6)	49.4(±11.9)	0.317†
Hemoglobin[a], g/dl	9.8(±2.3)	9.4(±1.5)	0.365†
Leukocyte[b], cell/mm^3	6190(1029-26060)	7055(1650-31670)	0.076‡
Platelet[b], thousand/mm^3	128.0(3.0-415.0)	80.5(34.0-677.0)	0.061‡
Ureum[b], g/dl	32.5(13.0-150.0)	33.5(11.0-302.0)	0.591‡
Creatinine[b], g/dl	0.8(0.3-9.5)	0.9(0.3-8.3)	0.274‡

Table 3. Laboratory parameters in liver cirrhosis † independent t-test; ‡ Mann-Whitney test; n: number; aMean(±SD); bMedian (min-max)

found that IL-6 in Child-Pugh C patients was at higher levels than Child-Pugh A (17). Upregulation of IL-6 and subsequent STAT3 regulatory cascades promote hepatic stellate cell (HSC) activation, causing liver fibrosis and cirrhosis (18). IL-6 could lead to excessive inflammatory activation that induces oxidative stress which is followed by tissue damage and liver disease progression (19). The activated HSC form a vicious cycle in the process of liver fibrosis. This condition is known as the inflammation-fibrosis-axis (20). Thus, IL-6 was associated with the severity of liver cirrhosis (17).

The association of different levels of pro- and anti-inflammatory cytokine with a type of hepatitis was also examined. HBV and HCV infections are characterized by inflammatory liver disease and an increased risk of developing cirrhosis. Host immune response and production of inflammatory cytokines are responsible for the liver injury (21). Changes in various cytokine activities are responsible for variable degrees of liver damage (22). Several studies found a positive relationship between IL-6 level and both HCV infection (23) and HBV infection (24). In HBV and HCV infection, Kupffer cells were involved in fibrogenesis by the release of IL-6, which induce HSC activation leading to liver fibrosis (25).

Studies also reported that increased serum IL-10 level has been found in HCV and HBV infections (22, 26). This cytokine regulates humoral immune response by downregulating the T helper 1(Th1) lymphocyte population and contributes to persistent infections (26). In the present study, no association was found between IL-6 and IL-10 and viral hepatitis. This could be attributed to the limitations of our study that we did not observe hepatitis staging, since both of these cytokines were prominent during the acute phase of infection (27).

A previous study showed that IL-23 played a role in T-cell immune response (28). It contributed to chronic inflammatory diseases (29) especially in both HBV and HCV infection (30). IL-23 was higher in the acute and chronic phases of HBV infection. Its expression was induced by the presence of HBsAg in HBV infection (31). In HCV infection, it seems that IL-23 could augment HCV infection mediated by dendritic cells and macrophages (32). IL-12 was considered to inhibit HBV replication by activating CD8 T cells with CD28 as a co-stimulator (33). Chronic hepatitis B patients had lower serum IL-12 levels (34). In this study, there was no difference in levels of IL-12 and IL-23 in subjects with viral hepatitis compare to non-viral hepatitis. This could be caused by the presence of IL-12 and IL-23 in other types of hepatitis such as autoimmune hepatitis (35) and alcoholic hepatitis (36).

Our study also elucidated the association between IL-6 and IL-23 levels and the presence of hepatic encephalopathy. Hepatic encephalopathy is a broad spectrum of neuropsychiatric disturbances associated with both acute and chronic liver failure. Mitochondrial energy disturbance caused by ammonia-induced neurotoxicity and increased brain cytokine flux by systemic inflammation is among the culprit of this condition (37).

The presence of higher IL-6 in patients with hepatic encephalopathy was also found in other studies. Luo et al. reported that IL-6 was involved in the pathomechanism of hepatic encephalopathy, of which hyperammonia was contributed (38). The lack of ammonia clearance provides IL-6 penetration through the blood-brain barrier, inducing edema of astrocytes and subsequent hepatic encephalopathy (39). As indicated by Wu et al., IL-6 was correlated with minimal hepatic encephalopathy via STAT3 activation that causing neural apoptosis (40). Moreover, Gyülvészi et al. showed that IL-23 might affect encephalitogenicity and CNS-tropism of effector T-cell through polarization of Th1 and Th17 cells resulting in neuroinflammation in CNS (41). On the contrary, IL-23 was found in lower levels in patients with hepatic encephalopathy in the present study. This finding shows that IL-23 could not be used as a prognostic marker to predict the presence of hepatic encephalopathy, as this cytokine could be affected by various other causes.

Renal failure in liver cirrhosis patients could be measured by abnormally high serum creatinine levels, which is associated with increased mortality (42). Hepatorenal syndrome (HRS) is one causative condition that leads to renal injury, caused by arterial underfilling due to splanchnic and systemic vasodilatation with high cardiac output. When circulatory dysfunction occurs, vasoconstrictor mediators are released, resulting in severe renal vasoconstriction (43). There is no significant association between liver cirrhosis severity and renal function abnormality. Ruiz-del-Arbol et al. observed that HRS developed in about 20% in 1 year and 40% in 5 years among patients with ascites (44).

There are several limitations to this study. We found only a small number of Child-Pugh A subjects, thus cytokine involvement in different stages of cirrhosis could not be analyzed. Autoimmune or other cause of cirrhosis was not analyzed. Future studies should be analyzing other inflammation-related biomarkers including CRP (C-reactive protein), TNF-α (tumor necrosis factor α), ROS (reactive oxygen species) metabolites, and NF-κB.

6. CONCLUSION

IL-6 level was associated with the severity of liver cirrhosis. Higher plasma IL-23 level was found in patients with no hepatic encephalopathy. There was no association between serum cytokines levels and hepatitis viral infection status.

- **Patient Consent Form**: The authors certify that they have obtained all appropriate patient consent forms.
- **Authors contribution**: I.R. gave a substantial contribution to the conception and design of the work. R.S. gave a substantial contribution of data. K.S. gave a substantial contribution to the acquisition, analysis, or interpretation of data for the work. I.R. had a part in article preparing for drafting or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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