Correlation Between Serum Thrombopoietin Level and Cirrhosis Clinical Stage in Liver Cirrhosis Patients in Mohammad Hoesin Palembang Hospital and Palembang BARI Hospital

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ABSTRACT

Background: *Thrombopoietin (TPO) is a cytokine mainly produced in the liver that regulate humoral control mechanism of thrombopoesis. Presumably, TPO production is decrease in patients with liver cirrhosis which interfere platelet production. The aim of this study was to identify the correlation between serum TPO levels and the clinical stage of liver cirrhosis.*

Method: *With analytical cross sectional design, this sudy analyzed the correlation between the serum TPO level and the clinical stage of liver cirrhosis according to Child-Pugh classification in 32 liver cirrhosis patients and 30 healthy subjects from March 2015 to August 2015. The serum level of TPO was examined using the Quantikine human TPO immunoassay.*

Results: *There were 13 females and 19 males patients aged 19 to 67 years old. Serum TPO level were lower in patients with liver cirrhosis (65.65 ± 28.97 pg/mL) than in healthy subjects (98.16 ± 41.25 pg/mL, $p < 0.005$). Serum TPO levels were negatively correlated with clinical stage of liver cirrhosis in a moderate strength of correlation ($r = -0.516$, $p = 0.002$). There were no correlation between serum TPO level and platelet count ($r = 0.186$; $p = 0.309$), but a significant negative correlation between the clinical stage of liver cirrhosis and platelet counts ($r = - 0.361$; $p = 0.042$).*

Conclusion: *There was a significant negative correlation between serum TPO levels and the clinical stage of liver cirrhosis according to Child-Pugh classification.*

Keywords: *liver cirrhosis, thrombopoietin (TPO), Child-Pugh classification*

ABSTRAK

Latar belakang: *Thrombopoietin (TPO) adalah sitokin yang diproduksi oleh hepar, berperan penting dalam pengaturan trombopoesis. Diduga bahwa produksi TPO akan menurun pada sirosis hati dan memengaruhi produksi trombosit. Tujuan penelitian ini adalah untuk mengetahui korelasi antara kadar TPO serum penderita sirosis hati dengan stadium klinik sirosis hati.*

Metode: *Penelitian analitik cross sectional ini menganalisis korelasi antara kadar TPO serum penderita sirosis hati dengan stadium klinik sirosis hati berdasarkan klasifikasi Child-Pugh pada 32 penderita sirosis hati dan 30 orang sehat dari bulan Maret 2015 sampai Agustus 2015. Kadar TPO serum diukur dengan metode Quantikine human TPO immunoassay.*

Hasil: *Subjek penelitian terdiri atas 13 orang perempuan dan 19 orang laki-laki, usia antara 19 tahun sampai 67 tahun dengan rerata usia 48,66 ± 11,80 tahun. Didapatkan bahwa rerata kadar TPO serum penderita sirosis hati lebih rendah dibandingkan dengan orang sehat (65,65 ± 28,97 pg/mL vs. 98,16 ± 41,25 pg/mL, p < 0.005). Kadar TPO serum berkorelasi negatif dengan stadium klinik sirosis hati dengan kekuatan korelasi sedang (r = -0,516; p = 0,002). Tidak terdapat korelasi antara kadar TPO serum dengan jumlah trombosit penderita sirosis hati (r = 0,186; p = 0,309). Stadium klinik sirosis hati berkorelasi negatif dengan jumlah trombosit dengan kekuatan korelasi lemah (r = -0,361; p = 0,042).*

Simpulan: *Terdapat korelasi negatif yang bermakna antara kadar TPO serum dengan stadium klinik sirosis hati berdasarkan klasifikasi Child-Pugh.*

Kata kunci: *sirosis hati, thrombopoietin (TPO), klasifikasi Child-Pugh*

INTRODUCTION

Liver cirrhosis was an end stage progressive condition of liver fibrosis marked with architectural distortion with the presence of regeneration nodule as a consequence of hepatocellular necrosis. World Health Organization (WHO) define liver cirrhosis histologically as diffuse liver disorder marked with fibrosis and alteration of normal liver tissue into abnormal nodules.[1-3] Liver cirrhosis cause 35,000 death annually in US and ranked as 7th cause of death worldwide. One of the commonly found complication of liver cirrhosis is bleeding that is dangerous, such as esophageal varices rupture. Esophageal varices were found in 50% liver cirrhosis patients and correlate to disease severity based on Child-Pugh classification. Upper gastrointestinal bleeding caused by esophageal varices rupture found in 5.5% Child A cirrhosis, 10.20% Child B cirrhosis, and 35.18% Child C cirrhosis, strongly associated with disease severity based on Child-Pugh classification.[3] Data on Kariadi Hospital (Semarang) and Soedarso Hospital (Pontianak) shown that esophageal varices rupture were cause of death in 25.8% and 59.7% liver cirrhosis patients, respectively.[1-3]

Thrombocytopenia was another serious complication of liver cirrhosis. Several mechanism was believed to cause thrombocytopenia in liver cirrhosis such as lower platelet production in bone marrow, shorter platelet cycle caused by autoimmune process by platelet-associated IgG (PAIgG), more platelet accumulation in spleen (splenomegaly), and lower thrombopoietin (TPO) production by hepatocyte as a consequence of liver cirrhosis.[4-6] TPO role both as cytokine and hormone to regulate megakaryopoiesis in platelet production. TPO was mainly produced by hepatocyte, and a smaller amount in kidney, spleen, lung, bone marrow, and brain. During hepatocyte inflammation, TPO production by hepatocyte were also decreased, so that serum TPO will reduce and interfere thrombopoiesis followed by platelet lysis.[7-9]

In liver cirrhosis patients, serum TPO were found to be lower than healthy individual and chronic hepatitis patients. Serum TPO level also correlate to clinical stadium according to Child-Pugh classification, the lower serum TPO the more severe its liver cirrhosis.[8-12] Otherwise, several studies (Temel et al, Stockelberg et al, and Yilmaz et al) showed that serum TPO in liver cirrhosis and liver fibrosis patients was not found to be lower than healthy individual and did not correlate to Child-Pugh classification.[8-16] Serum TPO were mainly regulated by total mass of platelet and circulating megakaryocyte by receptor mediated clearance mechanism.[17-19] TPO was a main regulator of platelet production, so that serum TPO become a recommended laboratory test to evaluate liver cirrhosis patients with thrombocytopenia.[20-28] Based on controversies in several studies above, author was realized the need of another study to know serum TPO level in liver cirrhosis patients and its correlation to Child-Pugh classification.

METHOD

This is a cross sectional study. Subject were divided into liver cirrhosis patients group and healthy individual matched by age and gender, than analyzed by correlative analytic observation. This study was conducted in Gastroenterohepatology Clinic and Ward in Dr. Mohammad Hoesin Hospital (Palembang) and Palembang BARI district hospital since March 2015 until finish in collaboration with Prodia Laboratory, Palembang. All patients fulfill inclusion criteria were chosen as sample. Inclusion criteria was liver cirrhosis patients diagnosed based on clinical manifestation, laboratory, and ultrasonography (USG) without account its etiology, both male and female, aged 18 years old above and willing to participate

in this study by signing the informed consent form. Exclusion criteria was sepsis, autoimmune disease, myeloproliferative disease, hepatoma, smoking, and acute coronary syndrome. Dependent variable was clinical stage of liver cirrhosis according to Child-Pugh classification and serum TPO level.

Subject blood laboratory studies was hemoglobin, leukocyte, erythrocyte sedimentation rate, differential count, blood glucose, ureum, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), HBsAg, anti-HCV, total serum protein, albumin, globulin, total bilirubin, prothrombin time, and international normalized ratio (INR). TPO test was using enzyme-linked immunosorbent assay (ELISA) microplate reader with Quantikine R Human TPO reagent. Data were taken in a research form and arranged in main table. Numeric variable descriptive analysis with normal distribution were presented as mean ± standard deviation, while data without normal distribution were presented as median (minimum value-maximum value). Test of normality was using Shapiro-Wilk test. Correlation between serum TPO and clinical stage of liver cirrhosis based on Child-Pugh classification were using Pearson test for normal distribution data and Spearman test for not normal distribution data.

RESULTS

Liver cirrhosis patients that fulfill the inclusion criteria was 32 patients, with Child-Pugh clinical stage of A, B, and C from any etiology. On the other hand, health samples were 30 individual matched with liver cirrhosis patients group based on age and gender. Demographic characteristic of study sample were shown in Table 1. Liver cirrhosis patients consist of 19 male subjects (59.4%) and 13 female subjects (40.6%) with 1,46:1 ratio. Mean age of liver cirrhosis group was 48.66 ± 11.80 years old and 48.09 ± 14.03 in healthy individual group. The most etiology of liver cirrhosis was hepatitis B with 21 patients (65.6%), hepatitis C with 9 patients (28.1%), and by another etiology in 2 patients (6.3%).

Laboratory characteristic of liver cirrhosis patients and healthy individual were shown in Table 2 and Table 3. From data shown above, it can be compared (cirrhosis patients vs. healthy individual) in mean hemoglobin level 9.99 ± 2.19 g/dL vs. 12.26 ± 1.72 g/dL, mean leukocyte count 8734.38 ± 5016.21/mm^3 vs. 6802 ± 2.198/mm^3, median platelet 105.000/mm^3 (48.000 – 150.000/mm^3) vs. 20.000 (153.000 – 509.000/mm^3), median blood glucose 127 mg/dL (92-184 mg/dL) vs. 119 mg/dL (82-168 mg/dL), median AST 49.50 U/l (12-160 U/l) vs. 29.00 U/l (18-60), median ALT 43.50 U/l (10-162 U/l) vs. 34.00 (18-72 U/l), and serum TPO 65.65 ± 28.97 pg/mL vs. 98.16 ± 41.25 pg/mL. In liver cirrhosis patients group, mean total protein was 6.17 ± 0.90 g/dL, mean albumin level 2.70 ± 0.66 g/dL, mean globulin level 3.30 g/dL (2.1-5.8 g/dL), median total bilirubin level 1.70 mg/dL (0.39-18.0 mg/dL), and mean INR 1.78 ± 0.59.

Table 1. Subjects characteristic

Characteristic	n (%)		Mean age	
	Liver cirrhosis patients	Healthy Individual	Liver cirrhosis patients	Healthy Individual
Gender				
Male	19 (59,40)	18 (60)	48,66 ± 11,80	48,09 ± 14,03
Female	13 (40,60)	12 (40)		

Table 2. Laboratory characteristics in liver cirrhosis patients group

Variable	Minimum	Maximum	Median	Mean ±SD
Hemoglobin (g/dL)	6,1	15,9	10,25	9,99 ± 2,19
Leukocyte (/mm^3)	2000	24600	7550	8734,38 ± 5016,21
Platelet (/mm^3)	48000	150000	105000	97968,75 ± 28591,09
Random blood glucose (mg/dL)	92	184	127	133,55 ± 27,42
AST (U/l)	12	160	49,50	58,06 ± 61,94
ALT (U/l)	12	160	43,50	49,59 ± 31,12
Total protein (g/dL)	5,0	8,2	5,90	6,17 ± 0,90
Albumin (g/dL)	1,4	4,4	2,60	2,70 ± 0,66
Globulin (g/dL)	2,1	5,8	3,30	3,46 ± 0,85
Total bilirubin (mg/dL)	0,39	6,60	1,70	2,21 ± 1,48
Bilirubin direct	0,16	5,70	1,16	1,46 ± 1,16
Bilirubin indirect	0,16	2,01	0,60	0,79 ± 0,30
Ureum (mg/dL)	16	110	50,00	46,22 ± 21,97
Creatinine (mg/dL)	0,5	2,1	0,98	1,07 ± 0,39
Thrombopoietin (pg/mL)	18,90	131,94	62,62	65,65 ± 28,97

AST: aspartate aminotransferase; ALT: alanine aminotransferase

Table 3. Laboratory Characteristic of Healthy Individuals Group

Variable	Minimum	Maximum	Median	Mean ± SD
Hemoglobin (g/dL)	9,20	15,70	12,30	12,26 ± 1,72
Leukocyte (/mm^3)	3400	12000	6650,00	6802,00 ± 2198,96
Platelet (/mm^3)	153000	5090000	209000	22466,67 ± 70776,03
Random blood glucose (mg/dL)	82	168,00	119,00	121,93 ± 17,97
AST (U/l)	18	60	29,00	30,53 ± 10,40
ALT (U/l)	18	72	34,00	35,83 ± 12,02
Ureum (mg/dL)	16,90	56,00	25,50	28,75 ± 11,08
Creatinine (mg/dL)	0,5	1,30	0,86	0,89 ± 0,19
Thrombopoietin (pg/mL)	36,58	212,27	101,71	98,16 ± 41,25

AST: aspartate aminotransferase; ALT: alanine aminotransferase

In this study, it was found 11 patients with Child-Pugh A (34.4%), 10 patients with Child-Pugh B (31.3%), and 11 patients with Child-Pugh C (34.4%). Serum TPO level in every clinical stage of Child-Pugh classification were shown in Table 4. Mean serum TPO level in more severe liver cirrhosis patients were found to be lower than less severe liver cirrhosis patients.

Table 4. Serum TPO level based on clinical stage of liver cirrhosis

Clinical stage of liver cirrhosis (Child-Pugh)	Thrombopoietin (TPO)	
	Median (minimum-maximum)	Mean ± SD
A	83,41 (39,97-131,94)	83,68 ± 28,10
B	59,83 (45-114)	65,28 ± 20,75
C	38,18 (19-95)	47,97 ± 26,90

Normality test in serum TPO level data showed a normal distribution, so that correlation between serum TPO level and liver cirrhosis clinical stage analyzed using Pearson Correlation test. Analysis showed a negative correlation between serum TPO level and liver cirrhosis clinical stages (r = -0.516; p = 0.002; n = 32), with moderate correlation strenght (r = 0.40-0.5999). it also showed no correlation between serum TPO level and platelet counts in liver cirrhosis patients (r = 0.186; p = 0.309; n = 32), showed in Figure 1.

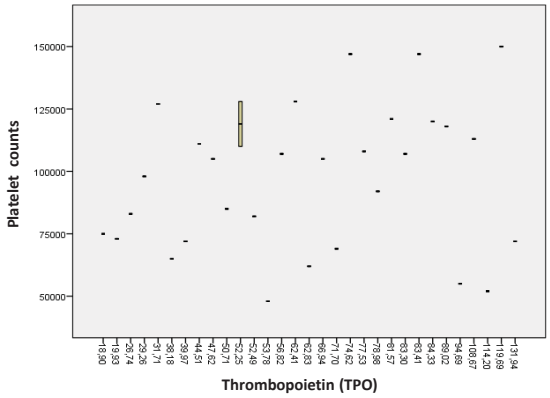

Figure 1. Distribution of serum TPO and platelet count correlation in liver cirrhosis patients.

Data also showed a negative correlation among clinical stages based on Child-Pugh classification and platelet counts in patients (r = -0.361; p = 0.042; n = 32). The strenght of its correlation was weak (r = 0.20-0.39).

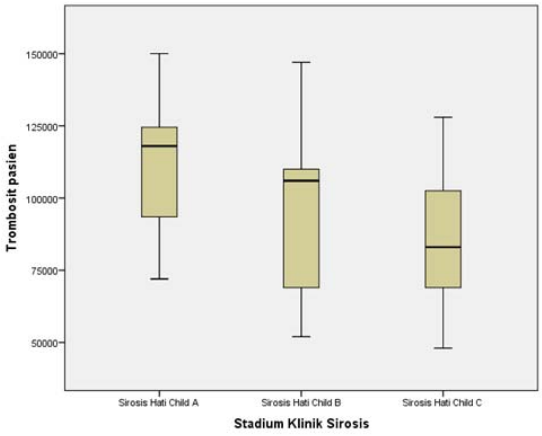

Figure 2. Distribution of platelet counts in different liver cirrhosis clinical stages

A comparison between mean serum TPO in different liver cirrhosis clinical stages showed insignificant differences, between Child A and Child B patients (83.67 ± 28.11 pg/mL vs. 65.28 ± 20.75 pg/mL; p = 0.421) and between Child B and Child C patients (65.28 ± 20.75 pg/mL vs. 47.97 ± 26.90 pg/mL; p = 0.234). Otherwise, a significant difference was found in comparison between serum TPO in Child A and Child C patients (83.67 ± 28.11 pg/mL vs. 65.28 ± 20.75 pg/mL; p = 0.047). In analysis between serum TPO level in liver cirrhosis patients and healthy population, a significant difference were found (65.56 ± 29.71 pg/mL vs. 98.16 ± 41.25 pg/mL; p = 0.002).

Otherwise, there were no significant difference in comparison of platelet counts between Child A and Child B liver cirrhosis patients (111636 ± 26934/uL vs. 95600 ± 28496/uL; p = 0.201), also between Child B and Child C liver cirrhosis patients (95600 ± 28496/uL vs. 86454 ± 26849/uL; p = 0.460). there

were significant difference in mean platelet counts between Child A and Child C liver cirrhosis patients (111,636 ± 26,934/uL vs. 86,454 ± 26,849/uL; p = 0.04). A comparison between platelet counts in liver cirrhosis patients and healthy individual groups showed a significant differences (97,733.33 ± 29,097.85 vs. 224,666.67 ± 70,996.03; p = 0.002).

DISCUSSION

In this study, male gender liver cirrhosis patients were found to be higher than female with 1,46:1 ratio. Mean patients age was 48.66 ± 11.80 years old. This result was similar to Hermono et al which reported that liver cirrhosis mostly found in 40-50 years old age group (mean age of 44 years old) with male to be found higher than female (ratio 2,1:1). Mean patients age in this study was different with Temel et al which reported 58 ± 10 years old age in liver cirrhosis patients. Factors that correlate to disease progressivity in chronic viral hepatitis was age in onset of infection, period of infection, gender, alcohol consumption > 50 grams per day, coinfection with hepatitis C and delta virus.[13,29,30]

Hepatitis B was found to be the etiology in most of liver cirrhosis patients in this study (65.6%), followed by hepatitis C (28.1%), and other underlying disease (6.3%). This data showed a difference in US liver cirrhosis etiology data which reported hepatitits C (26%), alcoholic liver disease (21%), and hepatitis C with alcoholic liver disease (15%) as the main cause of liver cirrhosis, while hepatitis B only cause 15% of liver cirrhosis. On the other hand, in Major European Countries, the main cause of liver cirrhosis was alcohol consumption followed by chronic hepatitis B infection. In Indonesia, it was reported that hepatitis B and C was the main cause of liver cirrhosis, in spite of alcoholic liver disease. WHO predicted that 3% (180 million people) of world population was infected by hepatitis C, 130 million among them has a risk to develop liver cirrhosis. Otherwise, chronic hepatitis B was accounted for 5-10%.[29,31,32]

Mean hemoglobin of liver cirrhosis patients in this study was 9.99 ± 2.19 g/dL, while in healthy individual group was 12.26 ± 1.72 g/dL. The lowest hemoglobin level found in this study was 6.1 g/dL. Anemia in liver cirrhosis patients was caused by folate deficiency, hypersplenism, alcohol intoxication, or gastrointestinal bleeding because of esophageal varises rupture.[30,33] Median Platelet in liver cirrhosis patients was 105,000/mm^3 (48,000-15,0000/mm^3), while median platelet in healthy individual patients was 209,000/mm^3 (153,000-509,000/mm^3). Thrombocytopenia condition was believe to be a good diagnostic marker in chronic liver disease and liver cirrhosis. Ibrahim et al and Afdal et al reported that chronic hepatitis C infection played an important role in reducing platelet production via TPO production suppression in hepatocyte, while pathogenesis between hepatitis C infection and thrombocytopenia was unknown yet.[11,12]

In severe liver cirrhosis, albumin level will decrease since its production was reduce in liver.[33] Mean albumin of all patients in this study was 2.70 ± 0.66 g/dL, with 3.15 ± 0.71 g/dL, 2.63 ± 0.35 g/dL, dan 2.32 ± 0.60 g/dL for Child A, Child B, and Child C liver cirrhosis patients, respectively. This result was close to Temel et al result with albumin level of 4.03 ± 0.59 g/dL, 3.04 ± 0.45 g/dL, and 2.44 ± 0.36 g/dL for Child A, Child B, and Child C liver cirrhosis patients, respectively.[13] Mean total bilirubin level in each clinical stage was 1.53 ± 1.10 g/dL, 2.11 ± 1.74 g/dL, and 2.98 ± 1.29 g/dL for Child A, Child B, and Child C liver cirrhosis patients, respectively. This result was similar to Tamel et al for Child A and Child B liver cirrhosis patients, with total bilirubin level of 1.29 ± 0.56 g/dL and 1.90 ± 0.97 g/dL, respectively. Hyperbilirubinemia in liver cirrhosis was caused by cholestatic condition, reduce of liver function, and reduce of renal excretion function.[30]

In this study, significant differences were found between serum TPO in liver cirrhosis patients and healthy individual population. Goulis et al compared serum TPO from 43 liver cirrhosis patients with 21 healthy population: 92.5 (20.3-286.3) pg/mL vs. 226.6 (30.1-848) pg/mL; p = 0.003).[9] In liver cirrhosis, serum TPO level will decrease because of its lower production on hepatocyte. Liver was the main organ to produce TPO to stabilize normal platelet counts, while kidney, spleen, lung, bone marrow, and brain also produces it on a smaller amount. In necrotic hepatocytes condition, TPO production would decreased, so that low thrombopoiesis could lead to platelet lysis. This theory were supported by several clinical data that showed serum TPO was increase following a orthopic liver transplantation procedure.[7-9]

In this study, serum TPO were reduce as the clinical stage were more severe according to Child-Pugh classification. But, in several case, patients with severe liver cirrhosis clinical stage were having higher serum TPO level. Pearson correlation test showed significant negative correlation between clinical stage of lier cirrhosis and serum TPO level, with moderate correlation (r = -0,516). It can be concluded that the

more severe liver cirrhosis, the ower serum TPO level. This result was similar to Adinolfi et al, Eisa et al, Afdal et al, and Ibrahim et al. In that study, serum TPO in liver cirrhosis patients was found to be lower than healthy individual groups and serum TPO level was negatively correlate to clinical stage of liver cirrhosis.[7-9]

This result as different to Temel et al that reported a serum TPO level (69 ± 12 pg/mL) that was higher than healthy individual (49 ± 9 pg/mL), no significant differences between serum TPO level in Child A, B, ad C liver cirrhosis clinical stages (64 ± 11 pg/mL; 75 ± 13 pg/mL; 68 ± 10 pg/mL), and no significant differences among all liver cirrhosis patients even with different etiology of cirrhosis. Temel believed that high serum TPO in liver cirrhosis patients compared to healthy individual were caused by constant production of TPO in liver, kidney, and bone marrow, while TPO use in circulation was reduce since TPO receptor in bone marrow were declined. [8-13]

There were no correlation between serum TPO level with platelet counts in liver cirrhosis patients ($r = 0.186$; $p = 0.309$; $n = 32$). This result was similar to Stockelberg et al, Goulis et al with correlation coefficient of $r = 0.47$; $p = 0.0015$, and Okubo et al that reported no correlation between serum TPO level and platelet counts in liver cirrhosis.[9,14,16] This result was different with Adinolfi et al that reported a positive correlation between serum TPO level and platelet counts in liver cirrhosis patients, showed by a low serum TPO level in thrombocytopenia patients rather than normal platelet patients. In contrast, Tamel et al reported that serum TPO was correlate negatively with platelet counts in liver cirrhosis patients ($r = -0.71$; $p < 0.001$). [10,13]

No correlation between serum TPO level and platelet counts in this study was believed to be caused by different factors underlie thrombocytopenia pathogenesis, and the main cause of liver cirrhosis in this study was chronic hepatitis B infection (65.6%) and hepatitis C viral infection (28.1%). A factors contribute to thrombocytopenia in liver cirrhosis patients was reduce platelet production in bone marrow because of hepatitis C infection.[8-12]

A significant negative correlation was found between liver cirrhosis cinical stage and platelet counts ($r = -0.361$; $p = 0.042$; $n = 32$), with weak correlation strenght ($r = 0.20$-0.39). This result explained that the more severe liver cirrhosis stages, the lower platelet counts in patients. This result was similar to Giannini et al, in study conducted at Italy and US with hepatitis C liver fibrosis sample, that showed a negative correlation between platelet counts and disease severity ($r = -0.498$; $p < 0.001$, and $r = -0.377$; $p < 0.001$), respectively.[34]

A comparison between mean platelet counts among different liver cirrhosis clinical stages showed a significant difference in Child A and Child C stages (111,636 ± 26,934/μL vs. 86,454 ± 26,849/μL ; $p = 0.040$). This result was similar to study in Temel et al conducted in Turkey at 92 liver cirrhosis patients that report a significant difference among Child A (134,358 ± 9,208/mm^3), Child B (92,416 ± 7,607/mm^3), and Child C (58,136 ± 5,476/mm^3), where the more severe liver cirrhosis clinical stage, the lower platelet counts. Analysis of comparison between mean platelet counts in liver cirrhosis patients and healthy individual groups showed a significant difference (97,733.33 ± 29,097.85 vs. 22,666.67 ± 70,996.03; $p = 0.000$). This result was similar to Tamel et al that reported a significant difference between platelet counts in liver cirrhosis patients and platelet counts in healthy population (97,000 ± 8,000/mm^3 vs. 240,000 ± 51,000/mm^3, $p < 0.001$).

CONCLUSION

A significant negative correlation was found between serum TPO level and liver cirrhosis clinical stage according to Child-Pugh classification. Mean serum TPO level were significantly lower than in healthy population. On the other hand, there were no correlation between serum TPO level and platelet counts in liver cirrhosis patients. A further study are need to investigate splenomegaly during the study protocol with upper gastrointestinal endoscopy.

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