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Medicine

COMPARISON OF SERUM VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) IN DEGREES CHILD PUGH SIROSIS PATIENTS

Faradilla Nova — Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia Haji Adam Malik General Hospital, Medan, Indonesia

Gontar Siregar* — Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia Haji Adam Malik General Hospital, Medan, Indonesia *Corresponding Author

Taufik Sungkar — Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia Haji Adam Malik General Hospital, Medan, Indonesia

ABSTRACT

Introduction: Liver cirrhosis is a pathological condition that describes the late stages of progressive liver fibrosis which is characterized by distortion of the liver architecture, as well as the formation of regenerative nodules. Liver cirrhosis is the most important risk factor in the development of hepatocellular carcinoma.Hepatitis B and C viruses are chronic viral infections that are proven as the etiology of liver cirrhosis and hepatocellular carcinoma. Child-Pugh scores can assess the general condition of patients with cirrhosis and assess multi-organ changes caused by cirrhosis of the liver. VEGF is a key signal used by oxygen-hungry cells to trigger blood vessel growth. VEGF is the main regulator of angiogenesis which works by stimulating mitogenesis from endothelial cells and increasing vascular permeability. Increased VEGF also occurs in the inflammatory process and damage to liver cells.

Method: The sample size for each study group are 20 people.The sample were diagnosed with Chirrosis Hepatic. patients were grouped according to the degree of Child Pugh A, B or C and then VEGF serum are perform.To display epidemiological data the subject of research used tabulation to show the descriptive picture. Data analyzed with SPSS 22nd.

Result: Based on the anova test, the result showed that VEGF levels were significance highly in the Child Pugh C group than Child Pugh B and A (p - value< 0.05)

Conclusion: There is a significant difference in serum VEGF levels between Child Pugh A, B, and C.

KEYWORDS : VEGF, Liver Chirrosis , Child Pugh

Introduction

Liver cirrhosis is a pathological condition that describes the late stages of progressive liver fibrosis which is characterized by distortion of the liver architecture, as well as the formation of regenerative nodules.[1]Liver cirrhosis is one of the important problems in the health sector because it can cause a variety of serious complications and require early treatment to improve prognosis and reduce mortality. More than 40% of patients with cirrhosis are asymptomatic and are often found during routine health checks and autopsi.[4,5]

Child-Pugh scores can assess the general condition of patients with cirrhosis and assess multi-organ changes caused by cirrhosis of the liver. Criteria for ascites and encephalopathy describe the degree of severity of portal hypertension, while other criteria, namely jaundice, albumin, and nutritional status describe the function of liver metabolism Then in 1973 R.N.H. Pugh changes the nutritional status criteria to PPT or INR, eliminating the most subjective criteria. The Child Pugh score is currently the most widely used score in clinical applications and is easy to apply.[6,7,8]

The Child-Pugh classification is related to survival. One-year survival rates for patients with Child A, B, and C respectively 100%, 80%, and 45%.Liver cirrhosis is a condition that describes the end stage of liver fibrosis where dead hepatocyte cells are replaced by fibrous connective tissue. The occurrence of fibrosis causes a state of hypoxia. The hypoxic state will stimulate the occurrence of angiogenesis which functions to regulate nutrient supply, growth factors and oxygenation of injured tissue (Makhlouf et al, 2002). One of the mediators that play a role in the process of vascular remodeling or angiogenesis, namely the Vascular Endothelial Growth Factor (VEGF).[9,10]

VEGF is a key signal used by oxygen-hungry cells to trigger blood vessel growth. VEGF is the main regulator of angiogenesis which works by stimulating mitogenesis from endothelial cells and increasing vascular permeability. Another function of VEGF is to regulate the permeability of microvasculae and tissue remodeling. VEGF is secreted by various types of cells such as muscle cells, glomelurus, choroid plexus, liver and platelets. The main regulators of VEGF expression are hypoxia, inflammatory cytokines, growth factors and hormonal. VEGF plays a role in the pathophysiology of chronic liver disease and this molecule often experiences hyperexpression in the early stages of liver fibrosis. Increased VEGF also occurs in the inflammatory process and damage to liver cells. In addition to hepatocyte cells, activated stella cells (which play a role in fibrogenesis) can also increase VEGF expression.[11,12]

The study of Abdoelmoaty et al reported that there was a difference in serum VEGF between Child Pugh scores wherein the results of serum VEGF levels were significantly increased in patients with Child pugh C compared to Child pugh A and B so serum VEGF levels could be assessed to see the prognosis liver cirrhosis.[13]

Angiogenesis is a very complex process, which is strictly regulated by proangiogenic factors such as VEGF and anti angiogenic factors. The occurrence of angiogenesis through several processes, among others: production of angiogenic growth factors by wound tissue binding to angiogenic growth factors on receptors in vascular endothelial cells, activation of pro-angiogenic molecular expression of endothelial cell genes, invasion of endothelial cells in surrounding tissue, cell migration and proliferation endothelium, formation of blood vessel lumen by endothelial cells, and stabilization of new blood vessels by mural cells. Important stages in the initiation of angiogenesis arise from changes in the balance between triggers and inhibitors, both increasing levels of triggers, decreasing levels of inhibitors or both.[14]

2. Method

2.1. Patient Selection

The research was conducted in a clinical trial with parallel design method with treatment group andcontrol group independently and randomized. Samples to be used in this study were all patients withthe diagnosis of Liver Chirrosis at Haji Adam Malik Hospital Medan starting from April 2018 until Juli 2019. The sample size for each study group is 20 people. Blood sampling was performed at the cubital fossa area of the study subjects for VEGF.

2.2. Inclusion criteria and exclusion criteria

Inclusion criteria, Subjects with age above 18 years both men and woman were diagnosed with Liver Chirrosis by USG abdomen. Subjects receive informed consent for physical and laboratory examination and finish desired by the Medical Research Ethics Committee of USU Medical Faculty.Exclusion criteria patients with systemic disease, Malignancy, Pregnant woman, the patient is not cooperative, and diseases that cause an inflammatory reaction.

2.3. Statistical Methods

To display epidemiological data the subject of research used tabulation to show the descriptive picture. Data was processed and analyzed using the SPSS 22nd program with a significance limit of p <0.05. Furthermore, normality data test was done with Kolmogorof smirnov. To compare serum VEGF levels between degrees of Child Pugh using the Anova test.

3.Result

In this study, 60 patients who met the inclusion criteria, more male sexes were 40 people (66.6%) than female sexes, namely 20 people (33.3%). The average age of patients is 53 + 7.8 years, cirrhosis of the liver is mostly suffered by the Batak tribe as many as 33 people (55%), followed by Javanese with 19 people (31.6%), Acehnese with 8 people (13.3%) The education level of most patients came from high school graduates as many as 24 people (40%), followed by elementary school graduates as many as 19 people (31.6%), junior high school graduates as many as 10 people (16.6%) and universities as many as 7 people (11, 6%). The majority of jobs were 22 employees (36.6%) as many as 18 people (30.0%), then IRT as many as 11 people (18.3%), and civil servants as many as 9 people (15.0%). The severity of cirrhosis of Child-Pugh A was found in 20 people (33.3%), Child pugh B was found in 20 people (33.3%) and Child Pugh C was as many as 20 people (33.3%). The mean serum VEGF level in patients with liver cirrhosis is 350.541 + 238.64.

Table 1. Baseline Characteristic in Liver Chirrosis Group

Characteristic	Liver Chirrosis (n = 60)
Gender, n (%)	
• Male	40 (66,6)
• Women	20 (33,3)
Age , mean± SD,years	53 ± 7,84
Tribe, n (%)	
• Bataknese	33 (55)
• Javanese	19 (31,6)
• Acehnese	8 (13,3)
Education level, n (%)	
• Elementary School	19 (31,6)
• Junior School	10 (16,6)
• High School	24 (40,0)
• Bachelor	7 (11,6)
Work, n (%)	
• Employe	22 (36,6)
• Enterpreneur	18 (30,0)
• Housewife	11 (18,3)
• Civil Servant	9 (15,0)
Degrees of Liver Chirrosis, n (%)	
• Child Pugh A	20 (33,3)
• Child Pugh B	20 (33,3)
• Child Pugh C	20 (33,3)
VEGF, mean ±SD, ng/ml	350,541± 238,64

In this study, serum VEGF levels were measured in liver cirrhosis patients between Child Pugh degrees (Child Pugh A, Child Pugh B, and Child Pugh C). The mean serum + SB VEGF in Child Pugh A is 138.4 + 91.78 ng / ml, while the mean + SB serum VEGF in Child Pugh B and Child Pugh C is 321.98 + 163.00 ng / ml and 591 , 24 + 180.65 ng / ml.

Table 2. VEGF Serum values for patients with cirrhosis of the liver between Child Pugh degrees

Child Pugh Degree	Mean ± SD	p value
Child Pugh A	138,4 ± 91,78	0,001
Child Pugh B	321,98 ± 163,00	
Child Pugh C	591,24 ± 180,65	

In table 2 shows VEGF levels that were statistically significant between the levels of the Child Pugh group (Child Pugh A, Child Pugh B, and Child Pugh C) (p = 0.001) .

Post Hoc test with Bonferoni method was done, the results showed that there were differences in VEGF levels that were statistically significant between the Child Pugh A group compared to the Child Pugh B group, Child Pugh A group compared to Child Pugh C, and Child Pugh B group compared to Child Pugh C (p = 0.001; p = 0,0001; p = 0,0001)

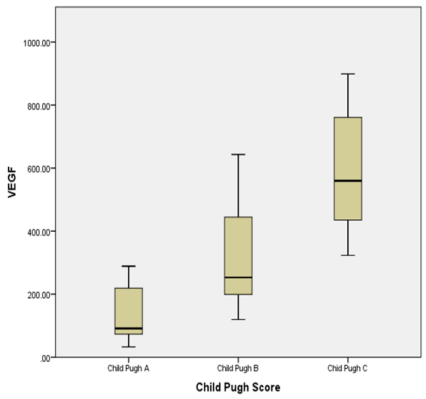

Figure1. Box Plot diagram VEGF level to the degree of Child Pugh

Table 3. VEGF Levels based on gender and age in HCC patients

Karakteristik	N	VEGF,median (min-maks)	P
Gender			
Male	40	317,75 (32,6-898,9)	0,347
Female	20	200,1 (72,9-822,4)	
Age			
>53 years	34	292,4 (32,6-898,9)	0,303
≤ 53 years	26	234,4 (59,9-580,2)	

Based on the Mann whitney test table, showed no significant difference for VEGF levels based on male and female sex or between the age group > 53 years and ≤ 53 years in patients with liver cirrhosis (> 0.05).

4. Discussion

In the results of this study it was found that VEGF levels tended to be higher in males than females although not significant (p = 0.347). The same study by Malamitsi et al and Kimura et al reported serum VEGF levels in adults by sex did not differ significantly (p> 0.05) (Malamitsi et al, 2000; Kimura et al, 2003). The results of this study also found that VEGF levels in liver cirrhosis did not differ significantly between the age group> 53 years and ≤ 53 years (p = 0.303). The same study conducted by Yamamoto et al. Analyzed 184 people from ages 21-59 years and reported no significant differences between VEGF levels and age (Yamamoto et al, 1996). Another study by Kumar et al analyzed 136 individuals from ages 20 to 80 years and reported no significant differences between VEGF levels and age (Kumar et al, 1998). This result is supported by Kaya et al. Reported no significant difference in VEGF levels based on age (P = 0.898).[15]

The most fundamental angiogenesis regulator known to date is VEGF. VEGF is a signaling protein that functions to restore oxygen supply to tissues when blood circulation is inadequate. The normal function of VEGF is to form new blood vessels during embryonic development (vasculogenesis), new blood vessels after an injury, muscle formation after an exercise and collateral circulation to pass the blocked blood vessels. The main physiological stimulation of VEGF production is hypoxia. In addition to physiological functions, VEGF also plays a role in pathological angiogenesis in tumor growth and inflammation.[7,8,9,16]

In liver cirrhosis VEGF expression tends to increase significantly when liver fibrosis occurs due to hypoxia and cell inflammation (Benvegnu et al, 2004). Liver fibrosis occurs because of an imbalance between extracellular matrix production and its degradation process, causing a decrease in sinusoidal perfusion in the liver (Muller, 2006). Decreased perfusion causes hypoxia. Factor-induced hypoxia HIF 1 is the main mediator for activating VEGF. Stelate cells that are in the perisinusoidal space are also important cells for producing extracellular matrices. Active stellate cells also have constricting properties. In addition to hepatocytes, activated stella cells (which play a role in fibrogenesis), are known to increase their expression of VEGF when activated. Injuries to the liver can also cause the migration of inflammatory cells that stimulate angiogenesis, which triggers increased levels of VEGF.[9,10]

The results of this study indicate that there are significant differences in serum VEGF levels between degrees of Child Pugh. The clinical

implications of the results of this study provide evidence that examination of serum VEGF levels can predict the severity of liver cirrhosis. Furthermore, in the Post Hoc analysis, this study showed that there was a significant difference in serum VEGF levels between Child Pugh A and B, Child Pugh A with C, and Child Pugh B with C. Therefore, serum VEGF levels could predict prognosis in patients. liver cirrhosis.[11,12,17]

Studies of VEGF levels in liver cirrhosis are still controversial. In this study it was found that VEGF levels in Child Pugh C were significantly higher than VEGF levels in Child Pugh A and B. This shows, the higher the severity of liver cirrhosis, the higher the VEGF levels. The same study was carried out by Abdelmoaty (2009) where the study compared VEGF levels of liver cirrhosis patients with Child Pugh degrees. It was reported that the VEGF level in Child Pugh A was 52.28 ± 9.5, Child Pugh B was 72.95 ± 15.3 and in Child Pugh C was 193.12 ± 24.2. There was a significant difference between Child Pugh A and Child Pugh B; Child Pugh A with Child Pugh C, Child Pugh B and Child Pugh C ($p < 0.005$). The highest concentration of VEGF was observed in patients with advanced stages of liver cirrhosis especially Child Pugh C. Therefore VEGF levels can be used to evaluate the prognosis[18,19,20]

5. Conclusion

Based on the results and discussion in this study, it can be concluded that there are significant differences in serum VEGF levels between degrees Child Pugh A, B, and C.

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