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RESEARCH

CORRELATION BETWEEN MATRIX METALLOPROTEINASE 1 SERUM LEVELS AND MODEL OF END STAGE HEPATIC DISEASE SCORE IN PATIENTS WITH HEPATIC CIRRHOSIS

(Kenasaban Kadar Matrix Metalloproteinase 1 Serum terhadap Skor Model End Stage Hepatic Disease di Pasien Sirosis Hati)

Stephanus Yoanito, Siti Muchayat

ABSTRAK

Sirosis hati masih menjadi masalah kesehatan utama di dunia, merupakan penyakit fibrosis hati yang berkebahayaan komplikasi. Pemeriksaan biopsi hati masih merupakan baku emas dalam penegakan diagnosis sirosis hati, tetapi pemeriksaan ini bersifat menyakitkan. Banyak model prognostik telah dikembangkan dalam dua dekade terakhir untuk meramalkan kematian di pasien sirosis hati dan variabel yang termasuk dalam model ini adalah Model End Stage Hepatic Disease (MELD). Penelitian ini mengukur kadar Matrix Metalloproteinase 1 (MMP-1) serum sebagai enzim dalam proses degradasi matrix extraselular pada sirosis hati, yang dapat digunakan untuk menilai tingkat keparahan di pasien sirosis hati. Tujuan penelitian ini adalah mengetahui korelasi kadar MMP-1 serum terhadap skor MELD di pasien sirosis hati. Penelitian ini menggunakan rancangan observasional potong lintang. Ciri subjek ditampilkan secara deskriptif dalam perbandingan. Ciri hasil laboratorium dalam bentuk rerata, simpang baku, median (minimum-maksimum). Uji Spearman digunakan untuk mengetahui kenasaban kadar MMP-1 serum terhadap skor MELD di pasien sirosis hati. Sebanyak 30 pasien sirosis hati, rerata umur 52,43 tahun, dominasi laki-laki sebesar 19 pasien (63,3%), penyebab terbanyak adalah HBV sebesar 18 pasien (60,4%), dengan nilai median skor MELD adalah 15,5 dan kadar rerata MMP-1 adalah 106,91 pg/mL. Terdapat kenasaban negatif moderate antara kadar MMP-1 serum dengan skor MELD dan bermakna dengan nilai r=- 0,402 (p=0,028). Terdapat kenasaban negatif moderate dan bermakna antara kadar MMP-1 serum dengan skor MELD di pasien sirosis hati. Untuk aplikasi klinis pemeriksaan MMP-1 serum dapat digunakan untuk memantau hasil pengobatan dan perjalanan penyakit pasien sirosis hati.

Kata kunci: *Matrix metalloproteinase-1, skor MELD, sirosis hati*

ABSTRACT

Hepatic cirrhosis is still a major health problem in the world and it has a great risk of complications. Hepatic biopsy is still the gold standard to diagnose hepatic cirrhosis, but it is invasive. Many prognostic models have been developed in the last two decades to predict mortality in patients with hepatic cirrhosis is Model End Stage Hepatic Disease (MELD). This study measured the levels of Matrix Metalloproteinase-1 (MMP-1) serum as the enzyme of extracellular matrix degradation process in hepatic cirrhosis that can be used to assess the severity of hepatic cirrhosis patients. The purpose of this study was to assess the correlation of levels of MMP-1 serum to MELD score in patients with hepatic cirrhosis. This study was a cross-sectional observational design. Subjects characteristics were presented descriptively in the proportions. Laboratory results characteristics were presented in mean, standard deviations, median (minimum and maximum). Spearman correlation was used to correlate the serum levels of MMP-1 to the MELD score in patients with hepatic cirrhosis. A total of 30 patients with hepatic cirrhosis, mean age 52.43 years, male predominance of 19 patients (63.3%), HBV was the most common cause of 18 patients (60.4%), with a median MELD score was 15.5 and the average level of MMP-1 was 106.91 mg/mL. A moderate negative correlation between serum levels of MMP-1 with MELD scores, r=-0.402 (p=0.028) was found. The presence of a moderate negative and significant correlation between serum levels of MMP-1 with MELD scores in patients with hepatic cirrhosis was found. For clinical application, examination of serum MMP-1 can be used to monitor disease progression and treatment outcomes of patients with hepatic cirrhosis.

Key words: Matrix metalloproteinase-1, MELD scores, hepatic cirrhosis

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INTRODUCTION

Hepatic cirrhosis and chronic hepatic disease are the 12th leading cause of death in the United States, in 2002, as many as 27.257 deaths (9.5 per 100,000 population) were reported, especially regarding males. In 2002, the World Health Organization (WHO), estimated that 783.000 patients in the world died from hepatic cirrhosis.[1] In Indonesia, data on the prevalence of hepatic cirrhosis nationally has not yet been reported, only reports of some education centers exist. The number of patients with hepatic cirrhosis in the Dr. Sardjito Hospital ranges from 4.1% per year out of the patients treated in the Department of Internal Medicine in the period from January to December 2002 were 301 cirrhosis hepatis patients.[2]

The prevalence of chronic HBV infection is more than 1% of the population in the world, with an estimated 300 million carriers. Infected hepatitis C Virus is about 100–300 million people in the world, approximately 20–25% of chronic hepatitis C become hepatic cirrhosis after a period of 10–20 years, while the prevalence of patients with hepatic fibrosis in the United States an estimated 360 patients per 100,000 people.[3]

Cirrhosis of the hepatic is defined as the final stages of hepatic fibrosis consequences which resulted in the formation of abnormal nodules and can alter hepatic function. Various etiological factors associated with chronic hepatitis among HBV or HCV, parasites, alcoholism, metabolic disorders for example α1-antitrypsin, ceruloplasmin deficiency, cystic fibrosis, autoimmune and drug intoxication.[4]

Examination of hepatic biopsy is still the gold standard in the diagnosis of hepatic cirrhosis. However, these tests are invasive, costly, need a have long time and frequent complications. Many prognostic models have been developed in the last two decades to predict mortality in patients with hepatic cirrhosis.

Model End Stage Hepatic Disease Score can be used to predict patients who will undergo Transjugular Intrahepatic Portosystemic Shunt (TIPS) therapy, as a tool for determining the priority of patients on waiting list who underwent hepatic transplantation/selected patients who will undergo a hepatic transplant and as a predictive factor deterioration of hepatic function and risk prediction mortality in cirrhotic patients.[5-7]

MELD score is composed of 3 bilirubin laboratory parameters, namely, the International Normalized Ratio (INR) and creatinine. MELD score is objective, all the parameters obtained from laboratory tests and are widely available, but it still takes some parameters into account and has some limitations.

Research on various parameters related to cirrhosis of the hepatic keeps continuing.[8] Definition of hepatic cirrhosis is morphologically characterized by diffuse fibrosis and conversion process of normal architecture of the hepatic becoming abnormal nodules structure. Hepatocyte necrosis and inflammation are chronic recurrent results in changes of hepatocytes enzymes, including Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) which is in blood; disruption to the metabolism of carbohydrates, proteins such as albumin and coagulation factor proteins and fats. Cytokines, chemokines of hepatocytes, biliary duct epithelial cells and leukocyte activation of HSC undergo transdifferentiation into myofibroblast changes in expression and secretion of extracellular matrix and deposition of extracellular matrix in between collagen.[8-10] Degradation of collagen is controlled by MMPs and tissue inhibitors inhibited by metalloproteinases matrix (TIMPs) and the increase in violent collagen serum levels is controlled.[11] TIMP-1 and TIMP-1/MMP-1 can be used as an index diagnosis of hepatic fibrosis in chronic hepatitis B virus infection. Role of TGF-ß1, TIMP-1 and MMP-1 and the ratio of MMP/TIMP as biomarker predictors of progression of chronic hepatitis activity and was supported by this current research.[11,12]

One of the genetic factors MMP-1 gene polymorphism as a key to decrease MMP-1 in hepatic cirrhosis, is the interaction of environmental factors with genetic variations in the progression of hepatic fibrosis research. Okamoto *et al.*[13] on MMP-1 gene polymorphisms 1G/2G, MMP-3 5A/6A, MMP-9 C/T found that matrix metalloproteinase have important role in the progression of hepatic fibrosis.[13]

This study aimed to investigate the correlation between the levels of Matrix Metalloproteinase-1 (MMP-1) serum with MELD score in patients with hepatic cirrhosis.

METHODS

This study design was a cross-sectional observational, performed in the Medicine wards, Gastro-Hepatology Clinic of the Dr. Sardjito Hospital and Clinical Laboratory, Dr. Sardjito Hospital, Yogyakarta for 12 months. Inclusion criteria were patients with cirrhosis of the hepatic with ultrasound diagnosis by clinicians who are hospitalized in the Internal Medicine ward and outpatient clinic of Gastro-Hepatology Dr. Sardjito Hospital, adult patients and who signed an informed consent. Exclusion criteria were patients with cirrhosis of the hepatic accompanied

by other diseases such as Diabetes Mellitus (DM), Chronic Kidney Disease (CKD), alcohol use in the last 2 weeks, gastrointestinal bleeding or blood transfusion in the last 2 weeks. Examination of MMP-1 is done by using ELISA method. Bilirubin measurements were performed by Diazo method. In this method, bilirubin reacts with Diazo reagent, assisted by caffeine, benzoate and acetate as accelerators, forming azobilirubin blue. The colour change was measured by a spectrophotometer at a wavelength of 520 nm. The normal value of total bilirubin is <1.1 mg/dL.

Creatinine measurement was done by Jaffe, it is creatinine in solution form the compound picric alkaline red yellow colour intensity can be measured by photometry. The normal value of creatinine for males is <1.2 mg/dL and for females is <0.9 mg/dL.

The principle of partial Prothrombin Time (PPT) was that Ca^{2+} ions in the blood are bound by an anticoagulant to prevent clotting. Plasma containing all the extrinsic coagulation factors (F.VII, Ca^{2+}) and common pathway (F.X, F.V, prothrombin and fibrinogen) except Ca^{2+} plus calcium-thromboplastin will form a clot. The process of clot formation is detected as a electromagnetic clot by the detector. Presentation of the results in the form of INR was performed by means of the calculation results PPT patients which were divided by mean normal plasma then raised to the value of the International Sensitivity Index (ISI) with the normal value of 0.8 to 1.2.

Analysis was conducted to test the validity of analytical precision compute averages, Standard Deviations (SD) and the Coefficient of Variation (CV). Accuracy test was conducted by test recovery. Characteristics of research subjects were displayed descriptively in proportion. Characteristics of the laboratory results were presented in mean, standard deviations, median (minimum-maximum). The correlation between serum levels of MMP-1 by the MELD score was tested by Pearson correlation test. Statistical calculations using a significance of $p<0.05$.

RESULTS AND DISCUSSION

In this study, patients with hepatic cirrhosis as many as 30 persons with an average age of 52.43 years and most were males in 19 patients (63.3%).

A research conducted by Chuan Lee *et al.*[14] showed similarities with this study, the mean age of patients with hepatic cirrhosis was 54 years of age, patients were more males than females and the alleged most common cause was the hepatitis B virus.[14] The study by

Table 1. Basic characteristics of the research subject

Variables	Frequency n=30	Proportion (%)
Age (years)	52,43±14,75	–
Gender		
Male	19	63.3
Female	11	36.7
Causes of hepatic cirrhosis		
Hepatitis B virus	18	60.4
cholestasis	10	33
Drug induced	1	3.3
Not known	1	3.3

Table 2. The Laboratory result of hepatic cirrhosis and MELD score

Variables	Mean ±SD/Median (min-max)
MMP-1 (μg/mL) (mean±SD)	106.91±59.78
MELD Score (median, min-max)	15.5 (7–35)
Creatinin (mg/dL) (median, min-max)	0.89 (0.45–23)
Bilirubin (mg/dL) (median, min-max)	2.56 (0.66–25.86)
International Normalized Ratio (median, min-max)	1.27 (0.76–2.68)

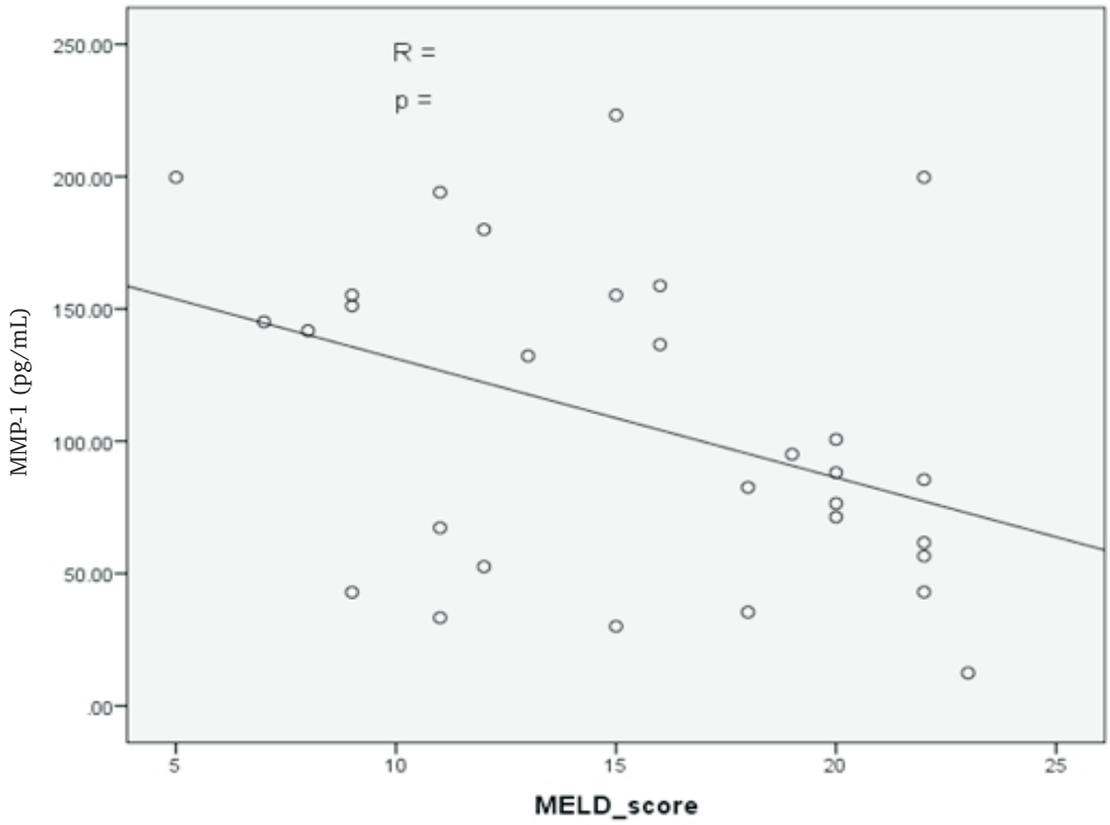

Figure 1. Correlation of serum levels of MMP-1 against the MELD score

Pleli *et al.*[15] with the results of hepatic cirrhosis patients with a mean age of 58 years, males more than females, with the most common cause was alcoholism. In alcoholic hepatic fibrosis was due to the accumulation of free radicals such as superoxide.[15]

Another study conducted by Gheorghe *et al.*[5] in patients with end stage hepatic disease undergoing hepatic transplantation obtained at a mean age of 45 years, most were males with the most cause of hepatitis virus.[5] A similar study conducted by Ghadir *et al.*[16] with ages between 41 and 50 years, more males than females and as the most common cause of HBV.[16] A research was conducted Dultz *et al.*[17] in patients with chronic hepatitis, mean age 51 years, males more than females.[17]

A research conducted by Chuan Lee *et al.*[14] showed that MELD score was 12, the mean bilirubin level was 2.1 mg/dL, the mean serum creatinine level was 1.1 mg/dL, mean INR value is 1.2.[14]

A research by Pleli *et al.*[15] found that the median MELD score was 14, creatinine levels of 1.03 mg/dL, INR value of 1.35 and a bilirubin level of 1.9 mg/dL.[15]

A research conducted Dultz *et al.*[17] in patients with chronic hepatitis, the mean value of MELD score was 9, the bilirubin levels of 1.12 mg/dL, INR value of 1.19 and a serum creatinine level of 0.84 mg/dL.[17] A research conducted by Moore *et al.*[18] stated that the higher the MELD score had an increased risk of death within 90 days. Patients with a MELD score <15 were less useful for a hepatic transplant. [18]

This research obtained a moderate and significant negative correlation between the levels of MMP-1 by the MELD score, with a value of r=-0.402 and p=0.028 (Figure 1).

A research conducted by Adel *et al.*[19] suggested that the serum levels of MMP-1 had a negative correlation with the degree of fibrosis.[19]

Limitations of this study were that did not checked the serial and the subjectivity of the examiner to look at the patient's clinical signs. In addition, this study had limitations in participating in the clinical assessment of patients, cirrhotic patients for clinical assessment including clinical factors constituent MELD score was left entirely to the clinician colleagues in the Department of Internal Medicine Dr. Sardjito Hospital.

CONCLUSIONS AND SUGGESTIONS

In this study there was moderate and significant negative correlation between serum levels of MMP-1 by the MELD score in patients with hepatic cirrhosis. For clinical applications, examination of serum MMP-1 can be used to monitor disease progression and treatment outcomes of patients with hepatic cirrhosis.

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