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DEGREE OF CHRONIC HEPATITIS C SEVERITY AND INSULIN RESISTANCE

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ABSTRACT

Background: *Diagnosis of fibrosis in chronic hepatitis C still needs invasive method such as liver biopsy. Aspartate Transaminase to Platelet Ratio Index (APRI) is a cheap and widely used assessment to indicate the presence of fibrosis in the liver. Insulin resistance as one an extra complication of chronic hepatitis C. We determined the correlation between degree of chronic hepatitis C severity based on APRI and the incidence of insulin resistance in chronic Hepatitis C patients.*

Methods: *Degree of chronic hepatitis C severity was determined based on APRI and insulin resistance were determined using HOMA-IR. Correlation were analyzed using Chi-square and phi coefficient test, respectively.*

Results: *Thirty chronic hepatitis C patients in this study consisted of in men was 16 male (53.3%) and 14 female (46.7%) patients with an average age of 51.63 ± 12.29. Frequency distributions of severity based on dominant APRI showed fibrosis in 18 patients (60%) and no fibrosis in 12 patients (40%). Insulin resistance distribution based on HOMA-IR showed no insulin resistance in 16 patients (53.3%) and insulin resistance in 14 patients (46.). There was a correlation between degree of chronic hepatitis C severity based on APRI and insulin resistance based on HOMA-IR with p = 0.006 and r = 0.491, respectively.*

Conclusion: *There was a correlation between chronic hepatitis C severity based on APRI and insulin resistance based on HOMA-IR*

KEYWORDS: *Chronic hepatitis C, degree of severity, insulin resistance*

INTRODUCTION

Hepatitis C virus infection (HCV) is one of the leading causes of acute and chronic liver disease. Acute hepatitis C infection that becomes persistent were about 85% of all cases (1)score related to reflux symptoms, and score related to dyspeptic symptoms and the evaluation of the quality of life was use the 8-item Short Form Health Survey in 2 categories, the physical component summary score and mental component summary score. All patients administered rabeprazole 10 mg/day for 8 weeks. We investigated the correlation between symptomatic improvement with proton pump inhibitor and quality of life. Significant symptomatic improvement was seen in the total score of 12 questions (26.7 ± 8.8 → 17.5 ± 5.9, p<0.0001.Based on the previous study, chronic hepatitis C patients will have two to three times of chance to experience insulin resistance and diabetes. This relates to the degree of hepatitis C severity that determined by the presence of liver fibrosis (2)Nigeria. METHODS Cross-sectional survey of 10 out of 120. Insulin resistance (RI) often occurs in patients with chronic hepatitis C, and this condition is correlated with advanced liver fibrosis by Vancouver Coastal Health (HCV) (3) infection and associated with fibrosis degree in chronic hepatitis C (4). Aspartate Transaminase-to-Platelet Ratio Index (APRI) is one of several noninvasive markers that have been introduced to measure cheap and widely available liver fibrosis (5)but excluded the substantial group

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of gastro-oesophageal reflux disease (GERD. However, until now, there has been no data linking the severity of chronic hepatitis C based on APRI with insulin resistance.

Based on epidemiological studies, chronic hepatitis C triggers about 27% of insulin resistance that will accelerate the progression of liver fibrosis, resistance to antiviral treatment and the development of hepatocellular carcinoma (6-9). Insulin resistance in chronic hepatitis C is reported to cause fatty accumulation in the liver, which activated virus replication that could ultimately exacerbate the response to anti-viral treatment, not only on hepatitis C genotype 1, also in genotypes 2 and 3 (10-12). Insulin resistance as one an extra complication of chronic hepatitis C (13) becomes a serious problem that needs to be known early on.

The mechanism of hepatitis C severity that causes insulin resistance is complex and not fully understood that depends on the HCV genotype. HCV genotype 1 could directly induce insulin resistance by interfering intracellular signaling in hepatocyte cells (14). Core proteins such asNS-3 and NS-5 are the major HCV protein components that are involved in the incidence of insulin resistance. During the occurrence of insulin resistance some pro-inflammatory cytokines and fat metabolism such as free fatty acid interfere with intracellular insulin signaling and trigger the occurrence of diabetes mellitus and steatosis (15). Hepatitis C treatment will improve the condition of insulin resistance (2). Various studies linking chronic hepatitis C infection to insulin resistance still use invasive methods of liver biopsy to assess fibrosis presence (8, 16-1 It is necessary to consider another method of assessing the severity of chronic hepatitis C-related insulin resistance.

The degree of severity of chronic hepatitis C is determined based on fibrosis manifestations in the liver. Assessment of the severity of hepatitis C could apply both invasive and non-invasive methods. Liver bio is a non-invasive method of percutaneous as a gold standard for assessing the degree of necro-inflammation (grading) and fibrosis (staging). Liver biopsy has several limitations and side effects such as pain and bleeding. In addition to the use of a small needle in the biopsy procedure resulted in very few tissues of representative liver samples. The variability between observers often results in 10 to 20% error in classification, depending on the scoring system u (20). At present, several noninvasive methods have been developed to determine the degree of liver fibros , including intransient elastography (FibroTest), APRI (aspartate aminotransferase (AST) to platelet ratio index) and FIB-4 (Fibrosis) (5, 21, 22). APRI is non-invasive, cheap and could be performed in almost all secondary and iary hospitals. APRI assessment results indicate the presence and absence of fibrosis in the liver. Based on this, the hors are interested in examining the correlation of chronic hepatitis C severity based on APRI and insulin resistance.

Methods

Subject: Thirty chronic Hepatitis C patients with Anti HCV (+) were enrolled in the sample at the outpatient unit of Gastro-Hepatology Dr.Soetomo General HospitalSurabaya. the data were collected from September 2015 to January 2016. The inclusion criteria were as follows; men and women, aged 18-65 , hepatitis C outpatients with a positive anti-HCV examination that lasted for 6 months by consent, no signs of acute hepatitis and no history of transfusion, no history of tattoos and syringes within 6 months, willing to participate this research by signing informed consent. The insulin fasting meter of the subjects was measure by using Immulite Series H.2711 (Immulite, Los Angeles, USA).

This was an observational analytic with cross-sectional approach. This research has obtained the approval of ethical clearance from the ethics committee of Dr. Soetomo Teaching Hospital, S abaya Indonesia. Characteristics of patients and HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) values for each degree of severity were presented in tables, graphs, d diagrams. Statistical analysis was significant if $p < 0.05$. For analysis was using Statistical Package for the Social Sciences (SPSS) software 20. (SPSS, Inc., Chicago, IL)

Results

The result of the 30 patients with chronic hepatitis C by sex was male by 16 (53.3%) patients and female by 14 (46.7% patients. Based on the age, it was known that the mean age of the patients in the study sample was 51.63 years with a standard deviation of 12.29 years, it means that most patients were aged between 39 and 64 years. (Table 1).

From the laboratory examination, mean of hemoglobin of 12.93 g% with standard deviation 1.95 was obtained. The average leukocyte obtained was 6.94 /uL with a standard deviation of 2.97. While the number of platelets obtained was normally distributed with a median value of 98.50 x 103 / uL with the lowest value range 0.75 x 103 / uL, and the highest was 331 x 103 / uL. From the serum transaminase examination, it was obtained that the distribution of very high values with abnormal distribution. The median value was SGOT 41.5 U/L with the lowest value range 15 U/L, and highest 308 U/L. The median value of SGPT was 60.5 U/L with the lowest value was 25 U/L and the highest was 342 U/L. From the examination of direct bilirubin, median value by 0.18 mg/dL with the lowest value 0,09 mg/dL and highest 5,87 mg/dL were obtained. While median bilirubin total was 0.66 mg/dL with the lowest value 0.14 mg/dL and highest 7.70 mg/dL. Blood albumin levels were still within normal limits with a mean of 3.79 ± 0.45 g/L (Table 1).

TABLE 1.

Characteristics of study subjects and Metabolic characteristics of study subjects

Variable	Frequency Abs	%	Mean	SD	Median
Sex			-		
Male	16	53.3%	-		
Female	14	46.7%			
Age (y/o)			51.63	12.29	
Hemoglobin (g%)			12.93	1.95	
Leukocytes (U/uL)			6.94	2.97	
Platelets (x 10^3/uL)			0.75 – 331		98.5
SGOT (U/L)			15 – 308		41.5
SGPT (U/L)			25 – 342		60.5
Direct Bilirubin (mg/dL)			25 – 342		0.18
Total Bilirubin (mg/dL)			0.14 – 7.70		0.66
Albumin (g/L)			3.79		0.45
BMI (Kg/m^2)					
Mean ± SD	21	70%	24	3.99	
Normal	9	30%	21,92	1.71	
Obesity	-	-	28,84	3.54	
GDP (mg/dL)			95.3	15.54	
Fasting Insulin (mU/L)			10.06	4.94	
Cholesterol (mg/dL)			171.7	39.81	

From the examination of Body Mass Index (BMI) was average value by 24.00 Kg/m2 with standard deviation 3.99 were obtained. Based on BMI calculation, 21 patients were classified as normal and 9 patients were classified as obese. The mean fasting patient's blood sugar level was 95.3 ± 15.54 g/dL. The measurement of GDP by mg/dL were converted to mmol/L in HOMA-IR calculations. The patient's fasting insulin level was measured after the patient performed a 12-hour fasting period of 10.06 ± 4.94 mU/L. From the assessment of blood cholesterol level mean 171.7 ± 39.81 mg/dL was obtained.

Degree of chronic hepatitis C severity based on Aspartate Transaminase-to-Platelet Ratio Index (APRI)

APRI values were obtained based on a formula calculation by using serum transaminase component and count of platelet from the subjects. Further assessment of the severity of chronic hepatitis C based on APRI with the following results. (Tabel 2) APRI value measurements from 30 subjects based on cut off 1.5 were 18 (60%) patients who had fibrosis with an average APRI value of 2.50 standard deviation by 1.39. However, patients without

TABEL 2.

Chronic hepatitis C severity based on APRI end Insulin resistance based on HOMA-IR

Variable		Frequency Patients abs	%	Mean	SD
APRI	Fibrosis	18	60	2.50	1.38
	non-fibrosis	12	40	1.02	0.37
HOMA- IR	Insulin Resistance	14	46.7	3.45	0.71
	No insulin resistance	16	53.3	1.45	0.61

fibrosis were 12 (40%) with an average value of APRI 1.02 and standard deviation 0.37 (Figure 1).

The incidence of insulin resistance based on Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) in chronic hepatitis C patients

Chronic hepatitis C patients examined by HOMA-IR has obtained the following results (Tabel 3). The results showed 14 (46.7%) patients have had experienced insulin resistance. The mean value of HOMA-IR patients with insulin resistance was 3.45 with a standard deviation of 0.71, while the patients without insulin resistance were 16 (53.3%) patients. The mean value of HOMA-IR patients without insulin resistance was 1.45 with a standard deviation of 0.61. (Figure 2)

Furthermore, the researchers wanted to know the correlation of obesity with insulin resistance in this study, that not obese patients obtained an average value of HOMA-IR 2.37 with a standard deviation of 1.30. While obese patients obtained an average value of HOMA-IR 2.41 with a standard deviation of 1.01. In the statistical analysis using chi-square comparison between obese and nonobese group did not get a significant correlation (p = 0.404). (Figure 3).

The correlation of chronic hepatitis C severity was based on APRI with insulin resistance based on HOMA-IR

The correlation examination between chronic hepatitis C severity based on APRI value and insulin resistance based on HOMA-IR was performed by relationship analysis. Where the researcher wanted to know the correlation of chronic hepatitis C severity that divided into; APRI values were categorized into fibrosis and without fibrosis based on the cut-off value of APRI and insulin resistance based on HOMA-IR in the subjects. (Figure 4)

TABEL 3.

Cross tabulation for APRI variables and Insulin Resistance

Variable		Insulin Resistance		
		None	Exist	Total
		HOMA IR		
		< 2.5	≥ 2.5	
APRI	Fibrosis	6	12	18
	Non- fibrosis	10	2	12
	Total	16	14	30

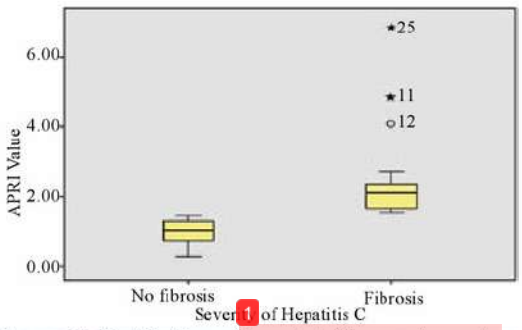

FIGURE 1. Distribution of Aspartate Transaminase-to-Platelet Ratio Index (APRI) Value

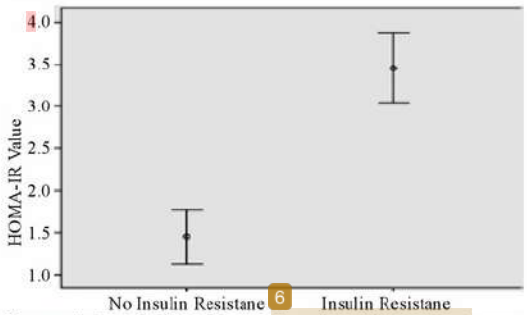

FIGURE 2. Insulin Distribution based on Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) Value

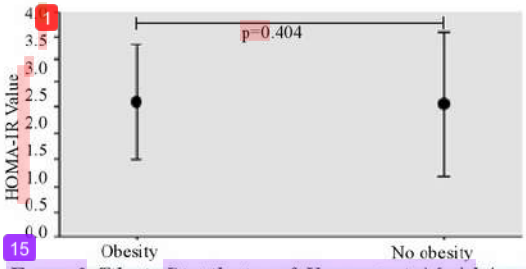

FIGURE 3. Tilapia Distribution of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) against Obesity

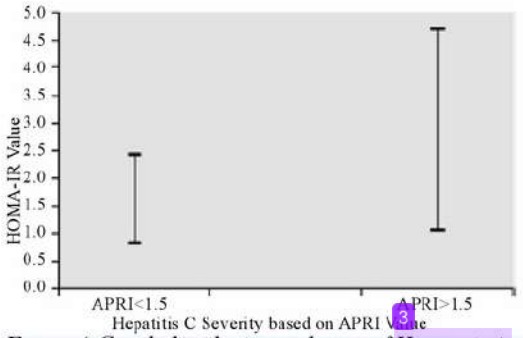

FIGURE 4. Graph distribution and mean of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) on chronic hepatitis C severity based on APRI

The test performed by Chi-Square (X2) hypothesis test because the data of chronic hepatitis C severity based on APRI and incidence of insulin resistance in chronic Hepatitis C patient were both nominal data types. Previously, cross-sectional data was presented to determine the number of each group. (Tabel 3) It was obtained from cross-tabulation between APRI variables and insulin resistance in patients with characteristic without fibrosis was more likely not to experience insulin resistance by 10 patients. While patients with the characteristics of fibrosis tend to experience insulin resistance by 12 patients. These results indicate an indication of the correlation between the degree of Hepatitis C severity based on APRI with insulin resistance based on HOMA-IR. Analysis of strong correlation was using phi coefficient test. Previously, the Chi-Square test requirement for the 2x2 table was no value e <5 (Yates Correction). In the table, it is known that no expectation value (e) was less than 5, therefore that chi-square test could be performed.

Discussion

The hepatitis C patients consisted of 16 (53.3%) men and 14 (46.7%) women. Chronic hepatitis C patients in male were higher than women. This due to several risk factors that in male patients was who has a tattoos and transfusion history. The incidence of hepatitis C in some Asian countries obtained a comparison of male hepatitis C: female 141: 122. The incidence of chronic hepatitis C patients was higher in male (2.1%) compared to female patients (1.1%) [23-25] Most of the studies and results reported the higher incidence of hepatitis C in men than in women, due to hepatitis C risk factors, such as higher injection drug use in men, and the risk of blood transfusion recipients (26-36).

Based on age characteristics, the mean age of patients was 51.63 ± 12.29 years. The results of this study are similar from some studies that reported the mean age of chronic hepatitis C patients was 41 ± 9 years, age group 20-29 years (30.94%), and 57.1 with age range 19-69 years (26,28,29). The youngest was 18-year-old that was found has a risk factor for tattooing. Risk factors for most of the study subjects received blood transfusions before 1992, the rest related to the use of injecting drug use and tattooing.

Calculation result based on Body Mass Index (BMI) was obtained 24.00 ± 3.99 Kg/m2 and 9 (30%) patients with obesity (BMI ≥ 25 Kg/m2). The researcher considerate of using 9 patient as research sample because of the difficulty in fulfilling the minimum amount of sample, it was supported by some previous studies that still involve obesity in the sample of their research, also (3, 11). The pathogenesis of obesity in chronic hepatitis C was correlated with inflammation, insulin resistance, steatosis, and the progression of fibrosis itself.

The subjects of this study were dominant with fibrosis by 18 (60%) patients and without fibrosis by 12 (40%) patients, also, the means value of APRI was 1.88 ± 1.34. It indicates that the majority of research subjects have already experienced fibrosis. This result differs from several other research that using the APRI method in assessing the severity of hepatitis C obtained the mean APRI0.71 ± 0.08 in 120 subjects of chronic hepatitis C genotype 1 and 2 (13).

The median value of APRI was 0.49 with a quartile root range of 0.43 in 108 chronic hepatitis C patients in Turkey (30). The difference in the results of this study with some other studies was due to differences in the number of samples and differences in hepatitis C virus genotypes affecting in fibrosis progression. This study did not examine the hepatitis C virus genotype.

It was reported insulin resistance was 14 (46.7%) patients and without insulin resistance was 16 (53.3%) patients. The mean value of HOMA-IR patients with insulin resistance was 3.45 ± 0.71, while value range of HOMA-IR patients with lowest insulin resistance was 2.65 to 4.71. This result was different from some other studies that reported the average HOMA-IR was 4.9 ± 1.69 out of the chronic hepatitis C patients (18). The incidence of insulin resistance in hepatitis C genotype 1 was 15 (65%) and genotype 3 was 12 (57%) (31). The incidence of insulin resistance 100 (38%) patients out of 263 chronic hepatitis C patients from the Asia was using the insulin resistance of HOMA IR> 2 (24). Hepatitis C was correlated with the incidence of insulin resistance compared to the control group (p = 0.02) (29). Thus, serial HOMA-IR testing of chronic hepatitis

C patients was one of the important biochemical indicators in the development of liver fibrosis. Insulin resistance was correlated with hepatitis C infection, especially genotypes 1 and 4 through the release mechanism of proinflammatory TNF-α inflammatory cytokines, in which TNF-α could interfere with signaling insulin by inhibiting phosphorylation in the IRS-1 and decreasing the release of GLUT-4 in muscle and fat tissue (32).

In this study, the value of HOMA-IR for severity with APRI ≥ 1.5 (fibrosis) has greater value than an APRI value <1.5 (without fibrosis). Where the mean value of HOMA-IR in patients with fibrosis was 2.89, and without fibrosis was 1.63. The average value of APRI was 0.71 ± 0.08. There was no significant difference in APRI values between chronic hepatitis C patients with insulin resistance and no insulin resistance (p = 0.839). This difference was due to the APRI value being the ratio scale that correlated with insulin resistance based on HOMA-IR (13).

Insulin resistance in chronic hepatitis C could possibility cause; hepatic steatosis, resistance to anti-viral treatment, liver fibrosis and oesophageal varicose, hepatocarcinogenesis and proliferation of hepatocarcinoma (33). Insulin resistance contributes to the progression of fibrosis in chronic hepatitis C (32). Insulin resistance triggers the progression of liver fibrosis in chronic hepatitis C patients with hepatic steatosis, hyperleptinemia, increased TNF production and reduced PPARI-γ release (23). The study did not investigate steatosis that was correlated with insulin resistance and fibrosis. Hepatitis C virus triggers insulin resistance through complex mechanisms. Decreased insulin signaling was preceded by an inflammatory response to hepatitis C virus, this process occurs in the phosphorylation of IRS insulin signaling tyrosine and the activation of phosphoinositide 3-kinase. Protein HCV enhances the release of TNF-α resulting from the proteasomal acceleration of IRS1 and IRS2 resulting in decreased insulin function resulting in the presence of insulin (34, 35). Interpretation of the correlation between the severity of chronic hepatitis C based on APRI with the incidence of insulin resistance in chronic Hepatitis C patients based on the p-value and strength of the relationship. In this study, the correlation between the severity of hepatitis C based on APRI with insulin resistance based on IR HOMA resulted in the p-value of 0.007 (Chi-square) less than 0.05 (α = 5%). Based on these results, the hypothesis of the study can be accepted, and it is concluded that there is a correlation between the degree of severity of hepatitis C based on APRI with insulin resistance based on HOMA- IR in chronic hepatitis C patients as the subject of this study.

In this study obesity as a confounding factor was included with the aim of closer to the actual reality conditions in the population and meet the minimum sample size of the study. Furthermore, the analysis of obesity with insulin resistance in chronic hepatitis C population was has no a significant correlation (p = 0.404). Therefore, obesity as a confounding factor was not very influential in causing insulin resistance in this study.

Hepatitis C virus has a direct effect on insulin signaling through the formation of hepatic steatosis at the beginning of insulin resistance. This condition was co-incidence in hepatitis C patients with risk factors for obesity and hyperlipidemia regardless of viral genotype. Hepatic steatosis might happen due to direct hepatopathy effects of HCV infection, especially genotype 3 (34). Hepatitis C genotype 3 patients have a wider steatosis but lower incidence of insulin resistance (14, 29, 36). Hepatitis C genotype 3a virus interferes with insulin signaling through the PPAR downregulation mechanism. In hepatitis C genotype 1b infection, insulin resistance occurs through the substitution mechanism of the amino acids 70 and/or 91 of the hepatitis C virus core protein genotype 1b (37). In this study genotype, hepatitis C virus was not performed to see the existence of genotype mechanism.

This study supports the hypothesis of a correlation hepatitis C severity based on APRI and insulin resistance based on HOMA-IR. We examine the degree of severity of hepatitis C based on APRI was based on easiness, inexpensiveness and practical that considered by clinicians in the field as an indicator of the onset of insulin resistance.

Conclusion

There was a correlation between chronic hepatitis C severity based on APRI and insulin resistance based on HOMA-IR Chronic hepatitis C patients with fibrosis will tend to experience insulin resistance, so evaluation of chronic hepatitis C severity based on APRI is important and considered for earlier intervention.

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