

CORRELATION BETWEEN HCV RNA VIRAL LOAD

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Correlation Between HCV RNA Viral Load And HOMA-IR In Chronic Hepatitis C Patients

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ABSTRACT

Introduction: Insulin resistance (IR) is one of the extrahepatic complications of hepatitis C virus (HCV) infection that needs to be recognized early. HOMA-IR is an effective way to measure insulin resistancy. Core proteins, NS-3, and NS-5 are the main components of HCV RNA proteins which are involved in the incidence of IR. Seeing this, a hypothesis was developed that the level of HCV RNA viral load was related to the HOMA-IR. This study was designed to identify the correlation between HCV RNA viral load with HOMA-IR in chronic hepatitis C patients.

Methods: We conducted a cross-sectional approach from the medical record of chronic hepatitis C patients at the outpatient clinic dr. Soetomo Hospital, Surabaya. A total of 30 patients aged >19 years old with complete medical records were included. Clinical and laboratory (including HCV RNA viral load level and HOMA-IR) data were obtained from the availability of medical records.

Results: A total of 30 chronic hepatitis C patients, 17 (56.7%) were women and 13 (43.3%) were men, with mean age was 50.90 ± 7.17 years. The median of HCV RNA viral load level was $3,14 \times 10^6$ IU/ml and the median of HOMA-IR was 4.50. The result of the Spearman correlation test showed a moderate positive association between HCV RNA viral load and HOMA-IR ($r=0.537$; $p=0.002$).

Conclusion: A positive moderate correlation was obtained between HCV RNA viral load with HOMA-IR in chronic hepatitis C patients.

Keywords: Chronic hepatitis C, HCV RNA viral load, HOMA-IR

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INTRODUCTION

Hepatitis C virus (HCV) infection is an important cause of liver disease in the world. Recent data estimates that 2.8% of the world's population - more than 184 million people - are infected with HCV. In 2016, WHO estimates that 399,000 people died from hepatitis C with various complications (Jafri & Gordon, 2018; Jefferies, 2018). Chronic hepatitis C is reported to be associated with a variety of diseases and complications, both intrahepatic and extrahepatic. Insulin resistance is one of the extrahepatic complications of HCV infection that needs to be recognized early because it can develop into other complications with serious consequences (Huang et al., 2011). HCV RNA protein is known to be involved in the development of insulin resistance in HCV infection (El-Zayadi & Anis, 2012).

Epidemiological studies show chronic hepatitis C triggers insulin resistance by 25% which will accelerate the progression of liver fibrosis, resistance to anti-viral treatment, and the development of hepatocellular carcinoma (Mohamed et al., 2011, Bernsmeiere & Heim, 2009; Mohamed HR et al., 2009; Bugianesi et al., 2005). Insulin resistance is a major pathogenetic factor of diabetes mellitus (DM) type 2 (Machado & Cortez-Pinto, 2009).

Several studies have reported that chronic hepatitis C patients have a threefold increased risk of developing insulin resistance and DM compared to healthy individuals or patients with hepatitis B virus infection (Huang et al., 2011). Liver cirrhosis is a diabetogenic disease. The risk of DM in cirrhosis associated with HCV is 3 to 5 times greater than in cirrhosis associated with other causes. The prevalence of DM in the population affected by HCV infection without liver cirrhosis is around 7.6 - 21%, which is 2 to 4 times higher than in other chronic hepatitis (White, 2008). One of the effective and efficient ways to measure insulin resistancy is the Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) (Romero-Gomez, 2006).

The components of the HCV RNA protein that are mainly involved in the occurrence of insulin resistance are core protein, NS-3 protein, and NS-5A protein. HCV core protein induces TNF- α expression, decreases VLDL, increases lipogenesis, thereby inducing insulin resistance (El-Zayadi & Anis, 2012). NS-3 protein has been shown to induce oxidative stress and increase NOX-2 regulation, thereby accelerating the production of ROS which ultimately leads to liver fibrosis and insulin resistance (Bureau et al., 2001). NS-5A protein induces endoplasmic reticulum (ER) stress that



leads to insulin resistance directly or indirectly by upregulation of the protein phosphatase 2A (PP2A) cellular gene (Christen et al., 2007). Looking at the involvement of HCV RNA protein components in the incidence of insulin resistance, a hypothesis was developed that the HCV RNA viral load was associated with an increased incidence of insulin resistance (Mohame et al., 2011).

The high prevalence of insulin resistance among patients with HCV infection has been consistently reported, and there is growing evidence to support this concept (Knobler et al., 2000; Mehta et al., 2000; Caronia et al., 1999; Mason et al., 1999). However, negative results regarding the association between HCV infection and insulin resistance have also been reported (Papatheodoridis et al., 2006; Mangia et al., 1998). The relationship between HCV RNA viral load and the incidence of insulin resistance remains controversial, while HCV RNA viral load examination is the initial routine check before starting therapy, so it is potential for screening insulin resistance in a large population of chronic hepatitis C. This study aims to analyze the correlation between HCV RNA viral load and HOMA-IR in patients with chronic hepatitis C thus it can predict the occurrence of complications of HCV infection, predict outcome of therapy, and assess prognosis of the disease from an early stage.

METHODS

This analytical observational cross-sectional study was conducted in the gastrohepatology outpatient clinic Dr. Soetomo Teaching Hospital, Surabaya. All medical records of chronic hepatitis C patients from September 2016 to January 2017, aged >19 years old were analyzed.

All patients who has been diagnoses of chronic hepatitis C and examined HCV RNA viral load, fasting blood glucose, and fasting insulin were included. Data of demographic, clinical, and laboratory were obtained from the availability of medical records. The study was approved by the Local Ethics Committee. All data analyzed statistically using SPSS version 23. For the normality test using the Kolmogorov-Smirnov test and then the data examined using Spearman correlation test.

RESULTS

A total of 30 subjects, 13 males (43.3%) and 17 females (56.7%), with chronic hepatitis C, aged >19 years old were analyzed as seen in table 1. Data that were normally distributed would be presented as mean \pm SD, while data that were not normally distributed would be presented as median (minimum value-maximum value). The mean age of the study subjects was 50.90 ± 7.17 years, the youngest was 36 years old and the oldest was 59 years old.

From the characteristics of the laboratory results, the mean hemoglobin was 13.37 ± 1.53 g%, the mean leukocyte was $5.670 \pm 1.725/\mu\text{L}$, and the mean platelet count was $187 \pm 74.45 \times 10^3/\mu\text{L}$. The mean value of AST was 86.70 ± 52.49 U/L and the mean value of ALT was 78.63 ± 38.88 U/L. Bilirubin examination revealed a wide range data with an abnormal distribution. The direct bilirubin examination obtained the median value was 0.61 mg/dL with the lowest value was 0.11 mg/dL and the highest value was 2.03 mg/dL. While the median of total bilirubin was 0.99 mg/dL, with the lowest value was 0.27 mg/dL and the highest was 2.52 mg/dL. Blood albumin levels were still within normal limits with a mean of 3.95 ± 0.31 g/L.

Table 1 Characteristic of Study Subjects

Variabel	n = 30	
	Mean \pm SD or Median (min-max)	
Age (years old)	50.90 \pm 7.17	
Haemoglobin (g%)	13.37 \pm 1.53	
Leukocyte (/ μL)	5.670 \pm 1.725	
Platelet ($\times 10^3$ / μL)	187 \pm 74.45	
AST (U/L)	86.70 \pm 52.49	
ALT (U/L)	78.63 \pm 38.88	
Albumin (g/L)	3.95 \pm 0.32	
Direct bilirubin (mg/dL)	0.61 (0.11 – 2.03)	
Total bilirubin (mg/dL)	0.99 (0.27 – 2.52)	
HCV RNA (IU/ml)	3.14 $\times 10^6$ (3.37 $\times 10^5$ - 3.91 $\times 10^7$)	

AST, aspartate aminotransferase; ALT, alanin aminotransferase; HCV RNA, hepatitis C virus ribonucleic acid

The metabolic characteristics of study subjects based on anthropometric data and laboratory (table 2). The median BMI of the study subjects was 23.76 (16.00 - 24.8) kg/m^2 . The mean abdominal circumference of male subjects was 84.07 ± 5.93 cm and female subjects was 75.23 ± 5.46 cm. The mean blood cholesterol level was 154.77 ± 27.18 mg/dL. The mean fasting blood sugar level was 101.03 ± 18.80 mg/dL. Fasting insulin levels were measured after the study subjects fasted for 12 hours and obtained a median of 12.88 (3.54 – 46.38) mU/L.

In this study, data collected on HCV RNA viral load levels and HOMA IR calculations based on fasting blood sugar and fasting insulin laboratory data from the medical records of 30 patients who were concluded. The number of HCV RNA viral loads in the subjects of this study was obtained median of 3.14×10^6 IU/mL, with the lowest level 3.37×10^5 IU/mL and the highest level 3.91×10^7 IU/mL. This study showed the value of HOMA IR subjects with a median of 4.50, with a minimum value range of 0.84 and a maximum value of 18.10.

Scatter plot of correlation between HCV RNA viral load level with HOMA IR value (Fig. 1) showed a positive linear relationship where the HOMA IR value tend to increase according to the increase in the number of HCV RNA viral load. Testing the significance level of the correlation between HCV RNA viral load and HOMA IR was carried out using the Spearman correlation test because the distribution of HCV RNA viral load data and HOMA IR value data were not normally distributed. Our study found that the result of Spearman correlation test showed a statistically significant positive correlation between HCV RNA viral load and HOMA IR ($r= 0.537$; $p= 0.002$).

Table 2 Metabolic Characteristic of Study Subjects

Variabel	n = 30
	Mean \pm SD or Median (min-max)
BMI (kg/m^2)	23.76 (16.00 – 24.8)
Abdominal circumference (cm)	
Male	84.07 \pm 5.93
Female	75.23 \pm 5.46
Cholesterol (mg/dL)	154.77 \pm 27.18
FPG (mg/dL)	101.03 \pm 18.80
Fasting insulin (mU/L)	12.8 (3.54– 46.38)
HOMA-IR	4.50 (0.84 – 18.10)

BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, homeostasis model for insulin resistance

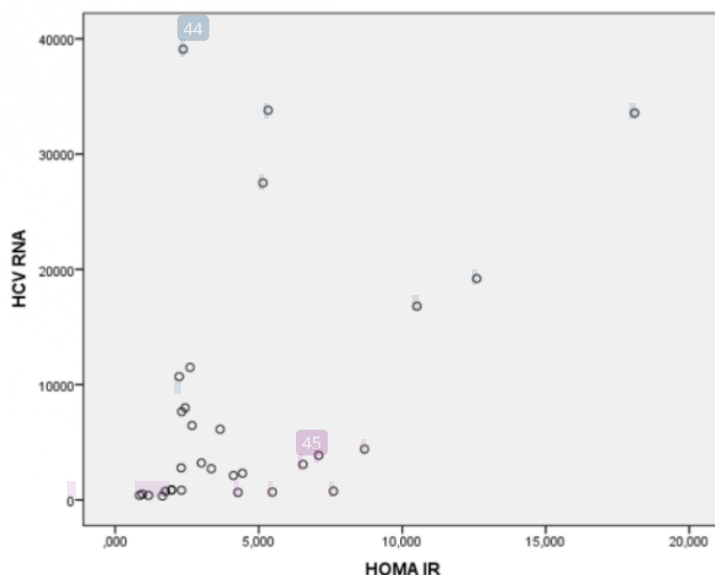


Figure 1. Scatter plot of correlation between HCV RNA with HOMA-IR

DISCUSSION

In this study, we conducted 30 secondary data in the form of medical records of chronic hepatitis C patients who had met the inclusion and exclusion criteria with a percentage of 13 males (43.3%) and 17 females (56.7%), with more female subjects. This result consistent with previous studies (Umumararungu et al., 2017; Olmedo et al., 2017). The transmission route of HCV infection in this study was mostly through family relationships, followed by a history of surgery, blood transfusions, and having tattoos. Meanwhile, data from Direktorat Jenderal Pengendalian dan Pencegahan Lingkungan (Dirjen P2PL) Indonesia in 2007-2012 showed that the highest number of cases was found in men, with the ratio of men and women is 83% : 17% and the transmission route was mostly in intravenous drugs users, then in hemodialysis patients, family with hepatitis C infection, and patients with blood transfusion history (Dirjen P2PL, 2017).

Differences in the results of this study can be caused by the difference of study methods, the inclusion and exclusion criteria used.

The acute manifestations of HCV infection range from asymptomatic (80%) to symptomatic (20%), both mild and severe. Patients who suffer from mild symptoms as well as those who are asymptomatic tend to ignore this disease and fall into a chronic condition. This causes the majority of chronic hepatitis C patients aged > 50 years (Dirjen P2PL, 2017). In this study, the mean age of subjects was 50.90 \pm 7.17 years old. The results of this study are not much different from previous studies (Niu et al., 2016; Vagu et al., 2013; Barut et al., 2012). In our study, the result of the mean fasting blood glucose of study subjects consistent with the previous study (Li et al., 2019; Aksu et al., 2012). The mean was 101.03 \pm 18.80 mg/dL. This result indicated that the

population in this study already had higher fasting blood glucose level than normal. Fasting blood sugar in HCV infection increased due to several reasons (Parvaiz et al., 2011). HCV RNA components, especially core protein, NS-3, and NS-5, the presence of excess iron, and the occurrence of liver fibrosis in HCV infection were some of the things that affect fasting blood sugar, so that affect HOMA IR value as well. Increasing fasting blood sugar can lead to insulin resistance.

HCV RNA viral load is the number of hepatitis C virus particles in every 1ml blood volume. Some of these virus particles are copies of the viral genetic material that circulates throughout the body. HCV RNA level of 800.000 IU/mL was considered as a high viral load level (Parvaiz et al., 2011). Some studies reported that high HCV RNA viral load level was consistently associated with high rates of infectivity and poor response to therapy. It was also associated with the development of hepatocellular carcinoma, liver problems related to hepatitis C infection, and a strong predictor of the occurrence of chronic kidney disease complications (Lai et al., 2017). The median of our study subjects' HCV RNA viral load was 3.14×10^6 IU/mL, with the lowest level was 3.37×10^5 IU/mL and the highest level was 3.91×10^7 IU/mL. The median indicated that the study subjects had a high level of viral load.

HOMA IR was the most commonly used method of insulin sensitivity assessment in the hepatitis C population. HOMA IR was chosen by author because it has nearly the same sensitivity as the hyperinsulinaemic-euglycemic glucose clamp (HIEG) method, which is the gold standard for measuring insulin resistance. HOMA IR is easier to perform than HIEG, relatively inexpensive, and is widely available (Peres et al., 2013). In this study we used a cut-off value of ≥ 2.5 in accordance with the cut-off value used by a study conducted in Taiwan, taking into account the similarities in the demographic location with Indonesia, namely from Asia (Huang et al., 2014). Our study showed the median of HOMA IR was 4.50 (0.84 – 18.10). It means that there was an incidence of insulin resistance in our study subjects. This result was supported by previous studies that chronic hepatitis C patients attend to have high value of HOMA IR (Aksu et al., 2012; Andrade et al., 2018; Gualerzi et al., 2018).

HCV infection causes insulin resistance through several mechanisms. One of the mechanisms is due to β -pancreatic cell damage and the presence of HCV RNA protein in the pancreatic tissue which causes direct cytopathic effects (Laskus et al., 1998). The components of the HCV RNA protein that are mainly involved in insulin resistance are the core protein, NS-3, and NS-5. HCV core protein induces TNF- α expression, decreases VLDL formation, increases lipogenesis and thus induces insulin resistance. The core protein also inhibits IRS-1, thereby decreasing GLUT4

regulation and increasing the release of PKC, a gluconeogenic enzyme (El-Zayadi & Anis, 2012). NS-3 protein has been shown to induce oxidative stress and increase NOX-2 regulation thereby accelerating the production of ROS and the release of pro-inflammatory cytokines such as TNF α , TGF β , IL-6, and IL-8, which ultimately lead to liver fibrosis and insulin resistance (Bureau et al., 2001). NS-5A protein induces endoplasmic reticulum (ER) stress that leads to insulin resistance directly or indirectly by upregulation of the protein phosphatase 2A (PP2A) cellular gene. PP2A itself decreases Akt regulation which results in inhibition of insulin signaling which leads to insulin resistance (Parvaiz et al., 2011).

The involvement of HCV RNA protein components in the incidence of insulin resistance was reflected in the relationship between HCV RNA viral load and HOMA IR. Our study showed a positive correlation with moderate strength between HCV RNA viral load and HOMA IR ($r=0.537$; $p=0.002$). Previous studies also found statistically significant correlation between the two. A high HCV RNA viral load level associated with high HOMA IR value indicated the incidence of insulin resistance in chronic hepatitis C patients, supported by others study (Hsu et al., 2007; Mucari et al., 2008).

This study has limitations because conducted with a cross-sectional design with one data collection chosen by author because it is relatively easy and the results are quickly obtained therefore unable to follow study subjects prospectively in analyzing the relationship between HCV RNA viral load and HOMA IR values in chronic hepatitis C patients. This study was conducted at the Gastrohepatology Outpatient Clinic Installation of Dr. Soetomo Teaching Hospital so that it did not describe the general public's situation.

CONCLUSION

The result of this study conclude that a positive moderate correlation was obtained between HCV RNA viral load and HOMA IR in chronic hepatitis C patients.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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