# Correlation Between Fibrosis-4 (FIB-4) Score and Metavir Score of Chronic Hepatitis C (CHC) Patients in Saiful Anwar Hospital Malang

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## ABSTRACT

***Background:*** *Hepatitis C still remain a serious problem in Indonesia lead to increasing prevalence , major morbidity and mortality. Liver biopsy is gold standar, invasive procedure for liver fibrosis staging for treatment monitoring and fibrosis regression. Fibrosis-4 (FIB-4) score has been proposed as a non-invasive, easy, inexpensive as alternative indirect marker for the assessment of liver fibrosis in chronic hepatitis C (CHC).*

***Method:*** *Analytical cross sectional study was conducted among 54 patients with CHC from 2012 -2017 in Saiful Anwar Hospital Malang. Subjects were examined for complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), anti hepatitis C virus (anti HCV), hepatitis C virus ribonucleic acid (HCV RNA), genotype, and performed liver biopsy. Statistical analysis was performed using Spearman test and statistical significant was assumed when $p < 0,05$.*

***Results:*** *Fifty four (54) patients were fulfilled the selection criteria from total 67 patients. 29 (53%) males, and 25 (47%) were females. The characteristic were 33 (61%) genotype 1, 12 (22%) genotype 2, 5 (9%) genotype 3, and undetermined 3 (6%); with means of HCV RNA titer 2,57 x 106, AST 79 ± 44 IU/L, ALT 77 ± 48 IU/L platelet 160.000/mm3. Distribution of Metavir F1 10 (19%) , Metavir F2 31(57%), Metavir F3 6(11%), and Metavir F4 7 (13%). Median of FIB-4 score as Metavir F1 1,88;Metavir F2 3,24; Metavir F3 5,36; Metavir F4 4,36. There was positive correlation between FIB-4 score and Metavir score ($r = 0.38$; $p = 0,01$).*

***Conclusion:*** *This study indicate that there was significant correlation between FIB-4 score and Metavir score in CHC patients.*

***Keywords:*** *Fibrosis-4 (FIB-4), Metavir, chronic hepatitis C, fibrosis*

## *ABSTRAK*

***Latar belakang:*** *Hepatitis C merupakan masalah yang serius di Indonesia, dengan peningkatan angka prevalensi, morbiditas dan mortalitas. Biopsi hati saat ini masih merupakan standar baku untuk menilai derajat fibrosis, monitoring pengobatan dan regresi fibrosis pada pasien hepatitis. Diperlukan marker penilaian derajat fibrosis pada pasien hepatitis C kronis yang bersifat non invasif, mudah , murah seperti penilaian dengan skor Fibrosis-4 (FIB-4).*

***Metode:*** *Studi analisis potong lintang pada 54 pasien hepatitis C Kronis yang memenuhi kriteria inklusi dari tahun 2012- 2017 di RS Saiful Anwar Malang. Pasien diperiksa darah lengkap aspartate aminotransferase*

*(AST), alanine aminotransferase (ALT), anti hepatitis C virus (anti HCV), hepatitis C virus ribonucleic acid (HCV RNA), genotipe dan dilakukan biopsi hati. Uji Statistik menggunakan korelasi Spearman dan bermakna signifikan dengan p < 0,05.*

***Hasil:*** *Lima puluh empat (54) pasien memenuhi kriteria inklusi dari total 67 pasien, 29 (53%) laki-laki , dan 25 (47%) perempuan. Karakteristik data didapatkan 33 (61%) genotipe 1, 12(22%) genotipe 2, 5 (9%) genotipe 3, and undetermined 3 (6%); dengan rata-rata HCV RNA titer 2,57 x 106 , AST 79 ± 44 IU/L, ALT 77 ± 48 IU/L platelet 160.000/mm3. Distribusi of Metavir F1 10 (19%), Metavir F2 31 (57%), Metafir F3 6 (11%), and Metavir F4 7 (13%). Median FIB-4 Sesuai Metavir F1 1,88; Metavir F2 3,24; Metavir F3 5,36; Metavir F4 4,36. Terdapat korelasi positif antara Skor FIB-4 dan Skor Metavir (r = 0.38; p = 0,01).*

***Simpulan:*** *studi ini menyimpulkan adanya korelasi positif antara skor FIB-4 dan skor Metavir.*

***Kata kunci:*** *fibrosis-4 (FIB-4), Metavir, hepatitis C kronis, fibrosis, derajat fibrosis*

## INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major public health problem, affecting an estimated more than 100 million with 3-4 million new cases each year. Patients infected with Hepatitis C virus have different clinical outcomes, ranging from acute resolving hepatitis to chronic liver disease including liver cirrhosis or hepatocelluler carcinoma.[1,2]

Liver fibrosis is a common pathological process of all chronic liver diseases, regardless of it causes, resulting from excessive accumulation of extracellular matrix. Estimating the degree of fibrosis has plays a very important role to monitor treatment or fibrosis regression.[3] The gold standard for fibrosis assessment is a liver biopsy. Because this procedure is invasive and has many limitations, including the risk of patient injury and error sampling, so non-invasive serum marker for liver fibrosis are being considered.[4,5]

FIB-4 score with components were age, aspartate aminotransferse (AST) serum level, alanine aminotransferase (ALT) serum level and platelet count has been proposed as a non-invasive, easy, cheap as alternative indirect markers for the assessment of liver fibrosis in chronic hepatitis C (CHC). The aim of this study was to know the correlation between FIB-4 score to metavir score in CHC patients.[4,5,6]

## METHOD

This study was conducted in Division of Gastroenterology and Hepatology, Department of Internal Medicine, Saiful Anwar Hospital, in the period between 2012-2017. A total of 67 patients with chronic HCV infection were enrolled in the study (Figure 1).

Inclusion criteria: (1) Patients diagnosed with CHC; (2) Agreed to perform liver biopsy. Exclusion criteria: (1) Patients with hepatocelluler carcinoma; (2) Patients with diabetes mellitus; (3) Patients with HBV-HIV co-infections; (4) Any other liver diseases; (5) Thrombocytopenia not related to portal hypertension. All patients were subjected to the following: history taking, through clinical examination, laboratory investigations including: complete blood count, liver function test, Hepatitis C virus antibodies using ELISA technique, HCV RNA and genotype of hepatitis C virus, and performed liver biopsy guided ultrasonography.

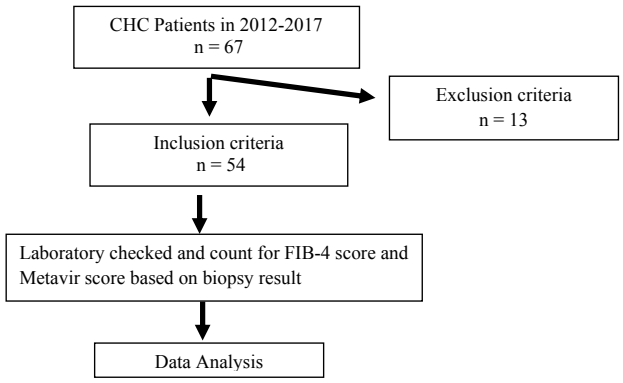


**Figure 1. Flow chart**

METAVIR scoring system was used to assess the necroinflamatory grades of activity and stage of fibrosis. There are 4 stage of fibrosis (F): (1) F0: no fibrosis; (2) F1: portal fibrosis without septa; (3) F2: portal fibrosis with rare septa; (4) F3: numerous septa without cirrhosis; (5) F4: cirrhosis. The FIB-4 score was calculated according to the formula:

$$\text{FIB4} = \frac{\text{Age (Years)} \times \text{AST (IU/L)}}{\text{Platelet count (109/L)} \times \sqrt{\text{ALT(UL/L)}}}$$

Results are expressed as absolute frequencies (%), means ± standard deviations, and medians (minimum – maximum). Correlation between FIB-4 and fibrosis

stages was estimated by spearman correlation indexes. And $p < 0.05$ was considered as statistically significant.

## RESULTS

Diagnostic model for liver fibrosis with non-invasive methods, has been published. Fifty-four patients fulfilled the selection criteria, Mean ages in these study was 58 ± 11 years old, Demographic and laboratory characteristics of these patients are summarized in table 1. 29 (53%) males , and 25 (47%) were females. The characteristic were 33 (61%) genotype 1,12 (22%) genotype 2, 5 (9%) genotype 3, and undetermined 3 (6%); with means of HCV RNA titer 2,57 x 106 , AST 79 ± 44 IU/L, ALT 77 ± 48 IU/L platelet 160.000/mm3. Distribution of Metavir F1 10 (19%), Metavir F2 31(57%), Metavir F3 6(11%), and Metavir F4 7 (13%).

**Table 1. Distribution of demographics characteristics and laboratory results**

| Characteristic | Chronic hepatitis C (n = 54) |
|---|---|
| Age | 58.76 ± 11.69 (mean ±SD) |
| Gender | |
| Male | 29 (53%) |
| Female | 25 (47%) |
| Genotype | |
| 1 | 33(61%) |
| 2 | 12 (22%) |
| 3 | 5 (9%) |
| 4 | 1 (2%) |
| Undetermined | 3 (6%) |
| Aspartate aminotransferase (AST) (IU/L) | 79.09 ± 44.37 (Mean ±SD) |
| Alanine aminotransferase (ALT) (IU/L) | 77.48 ± 50.68 (Mean ±SD) |
| Platelets(/mm$^3$) | 160.000 (Mean) |
| Hepatitis C virus ribonucleic acid (HCV RNA) | 2.57 x 10$^6$ (Mean) |
| Metavir | |
| F0 | 0 (0%) |
| F1 | 10 (19%) |
| F2 | 31 (57%) |
| F3 | 6 (11%) |
| F4 | 7 (13%) |

## DISCUSSION

Previous study by Farenci et al showed that FIB4 index, provides a valuable, non-invasive measure of fibrosis and can be used to predict virologic response in patients treated with ribavirin in chronic hepatitis C patients. The distribution of metavir in F1 (male : female = 6:4), F2 (male : female = 14 : 17 and F3 (male : female = 3 : 3) were equal in both gender but in contrary in F4 the highest prevalence was male (male : female = 6: 1) (Table 2).7 It was also shown that male patients were more likely to suffer from advanced fibrosis at a than female patients, which is not surprising given that male patients generally tend to have more severe liver diseases of most etiologies compared with females. In general, men are more likely to die from chronic liver disease and cirrhosis than are women.8 This phenomenon may be explained by the protective effect of female sex hormones on the progression of hepatic fibrosis.

Various potential mechanisms include the effect of sex hormones on oxidative and metabolic pathways, differential gene transcription in response to injury in women compared with men, and sex differences in immune regulation.8 Women clear acute hepatitis C virus (HCV) infection at a higher rate than do men.9 Estrogen may have a protective role against fibrosis in viral hepatitis by inhibiting stellate cells, which are responsible for fibrogenesis in the liver.10

**Table 2. Distribution of gender according to fibrosis stage**

| Metavir | Males | Females | Total |
|---|---|---|---|
| F1 | 6 | 4 | 10 |
| F2 | 14 | 17 | 31 |
| F3 | 3 | 3 | 6 |
| F4 | 6 | 1 | 7 |

From all patients, the highest prevalence is genotype 1. Its equal with study by Niu (2016) and Sievert (2011) about epidemiology Hepatitis C in Asia and Australia that said, distribution of genotype, mostly is genotype 1.11

Fib-4 score, we found increasing number of median equal with inceasing fibrosis degree of Metavir score, but we found it decrease in F4, although it still relate

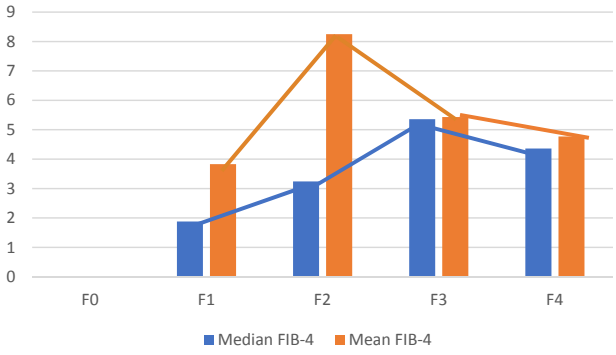


**Figure 1. Histogram of median and mean fibrosis-4 (FIB-4) score to metavir score**

with severe fibrosis, as previous study that mention FIB-4 > 3.25 equal with severe fibrosis (F3-F4).

Spearman test was done to identify correlation between FIB-4 score and fibrosis degree with metavir in CHC patient, the result was positive correlation with eventhough its weak (r = 0,38), with significant p = 0.01 ($p < 0.05$). Platelets count decrease and AST leves increase with the progression of liver fibrosis. Platelet generation diminished secondary to a decreased

production of thrombopoeitin by hepatocytes.12 Also, platelets are sequestred and destructed in the spleen as liver fibrosis advances and portal hypertension develops.13 As to AST, ongoing liver injury increases its release from mitochondria, and fibrosis decreases its clearance.

Our study have several limitations, includes small sample size, so the data distribution were abnormal. In summary, in our CHC patients, the FIB-4 score can be a useful as non-invasive methods for liver fibrosis and cirrhosis prediction, especially in limited sources, when liver biopsy and fibroscan facility were unavailable and contraindicated.

## CONCLUSION

This study indicate that there was significant correlation between FIB-4 score and Metavir score in CHC patients.

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