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The Value of Indirect Biomarkers in the Monitoring of Hepatitis C Virus Infection at the Mogadishu Hospital, Somalia

Somali Mogadişu Hastanesinde Hepatit C Virüsü Enfeksiyonunun İzlenmesinde Dolaylı Biyobelirteçlerin Değeri

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ABSTRACT

Aim: We aimed to investigate the value of Class II fibrosis markers as predictors of liver disease progress, and changes in platelet parameters in the laboratory tests of patients with Hepatitis C virus infection [anti-HCV (+)]admitted to the Somalia Mogadishu Hospital.

Material and Methods: All patients older than 18 years old, who were examined in our hospital's were included in the study. Accompanied by CBC and biochemical measurement results from patients, indirect liver fibrosis (Class II) markers AAR (AST/ALT ratio), APRI (AST/Plt ratio index) and FIB-4 index (Age (year) x AST (U/L) / [Platelet count (109 / L)] x (ALT) 1/2 (U / L)], MPV/Platelet ratio, APRI = [(person AST/AST reference upper limit) x Platelet (103 /ml) x 100] were calculated.

Results: A total of 2,887 patients, 1,605 (55.6%) male and 1,282 (44.4%) female, with a median age of 51 (32-67) years, were included in our study. The anti-HCV positivity rate was found to be 1.5 times higher in men than women.APRI, MPV / Plt R and RPR levels, indirect markers of liver damage, were found to be higher in patients with anti-HCV (+) than those in the control group (p<0.001).The median FIB-4 value of anti HCV (+) patients was found to be 1.94 (0.07-297.41).

Conclusion: We think that APRI, MPR, the MPV/Plt ratio and FIB-4 biomarkers in particularare useful tests in indicating fibrosis and in predicting its severity in patients with anti-HCV (+) in the Sub-Saharan Africa region.

Keywords: Anti-HCV, MPV/Plt ratio, AAR, APRI, FIB-4

ÖZ

Amaç: Somali Mogadişu Hastanesi'ne başvuran Hepatit C virüsü enfeksiyonu [anti-HCV (+)] olan hastaların laboratuvar testlerinde, karaciğer hastalığının ilerlemesini öngören Sınıf II fibrozis belirteçlerinin değerini ve trombosit parametrelerindeki değişiklikleri araştırmayı amaçladık.

Gereç ve Yöntemler: Hastanemizde muayene edilen 18 yaş üstü tüm hastalar çalışmaya dahil edildi. CBC ve hastalardan alınan biyokimyasal ölçüm sonuçları eşliğinde, dolaylı karaciğer fibrozu (Sınıf II) belirteçleri AAR (AST/ALT oranı), APRI (AST/Plt oran indeksi) ve FIB-4 indeksi (Yaş (yıl) x AST (U/L)) / [Platelet sayısı (109 / L)] x (ALT) 1/2 (U / L)], MPV/Platelet oranı, APRI = [(kişi AST/AST referans üst limiti) x Trombosit (103 /ml) x 100] hesaplandı.

Bulgular: Çalışmamıza medyan yaşı 51 (32-67) yıl olan 1.605 (%55.6) erkek ve 1.282 (%44.4) kadın olmak üzere toplam 2.887 hasta dahil edildi. Erkeklerde anti-HCV pozitiflik oranı kadınlara göre 1,5 kat daha yüksek bulundu. Karaciğer hasarının dolaylı belirteçleri olan APRI, MPV / Plt R ve RPR düzeyleri, anti-HCV (+) olan hastalarda kontrol grubuna göre daha yüksek bulundu (p<0,001). Anti HCV (+) hastaların medyan FIB-4 değeri 1,94 (0,07-297.41) olarak bulundu.

Sonuç: Özellikle APRI, MPR, MPV/Plt oranı ve FIB-4 biyobelirteçlerinin Sahra Altı Afrika bölgesinde anti-HCV (+) olan hastalarda fibrozisi göstermede ve şiddetini tahmin etmede faydalı testler olduğunu düşünüyoruz.

Anahtar Sözcükler: Anti-HCV, MPV/Plt oranı, APRI, FIB-4

INTRODUCTION

Hepatitis C virus (HCV) infection, a major clinical and public health problem affecting more than 71 million people worldwide, is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) (1). In Southeast Asia alone, it is known that more than 30 million people have chronic HCV infection, and the number of HCV (+) patients in Sub-Saharan Africa accounts for almost a fifth of the total global number (2).

In recent prevalence studies conducted in Somalia, the overall HBV prevalence was found to be 18.9% (95% CI: 14% to 29%) and the HCV prevalence was found to be 4.84% (95% CI: 3.02% to 7.67%). Therefore, the most common cause of chronic viral hepatitis following HBV infection is HCV (3). As a result, the burden of chronic HCV infection on the health system is significant. Treatment of the disease is possible with necessary screening and early antiviral treatments. Treatment resultsare more promising in cases that have not progressed, and the development of chronic liver disease (cirrhosis, HCC, hepatosteatosis) can be significantly reduced.

The golden standard in evaluating liver histology and the severity of fibrosis in patients with chronic viral hepatitis is still considered to be the liver biopsy (4). However, its use in some patient groups is limited due to its being expensive, invasive, requiring adequate technical infrastructure, and its rare, but potentially life-threatening complications (5).

As a result of these difficulties, there are some indirect biomarkers (Class II) that can be easily measured, that are inexpensive, reproducible and can be calculated with routine laboratory tests to evaluate liver damage in patients with chronic hepatitis. These include AST, ALT, GGT, bilirubin, apolipoprotein A1, haptoglobin and α-2 macroglobulin.

In addition, several combined serum biomarkers obtained through laboratory tests can be used:APRI [aspartate transaminase (AST) / platelet count ratio index] score, Fibrosis-4 (FIB-4) score, AAR [AST / alanine transaminase (ALT) ratio],red cell distribution width (RDW) / platelet count ratio (RPR) and mean platelet volume (MPV).

In this study, we aimed to investigate the value of Class II fibrosis markers as predictors of liver disease progress, and changes in platelet parameters in the laboratory tests of patients with Hepatitis C virus infection [Anti-HCV (+)] and in those of the control group admitted to the Somalia Mogadishu Turkish Hospital.

MATERIAL and METHODS

Patients

This study was planned as a retrospective case-control study evaluating chronic HCV-infected patients and a control group between January 2017 and June 2019.

This study was initiated after the approval of the local Ethics Committee of the Mogadishu Somali Turkey Recep Tayyip Erdogan Training and Research Hospital (07.08.2019 MSTH/1815), and we obtained informed consent from all participants.

All patients older than 18 years old, who were examined in our hospital's polyclinics were included in the study. Where anti-HCV (+) was found, this was taken as an indication of HCV infection given the conditions at our hospital, while those who had similar characteristics to the patient group and were anti-HCV (-), based on tests performed at our hospital, were evaluated as the control group in our study.

Intravenous peripheral blood samples from the patients were taken into standard purple-capped tubes containing dipotassium ethylene-diamine-tetra-acetic acid (EDTA) before angiography. An automatic blood count device (Sysmex XN-1000 Sysmex Corporation, Kobe, Japan) was used to count all CBC samples. Since dipotassium EDTA may cause changes in platelet volume and number, analyzes for optimal CBC measurement were performed within the first 30 minutes after blood collection.Serum aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, albumin and the levels of other routine biochemical parameters were measured using automated techniques (Mindray BS-800 Chemistry Analyzer, Shenzhen, China, Mindray BS-400 Chemistry Analyzer, Shenzhen, China).

Laboratory Measurements

Patients with underlying diseases such as co-infection with HBV, coronary artery disease and inflammatory rheumatic disease, with a history of splenectomy, diagnosed cardiac disease, renal dysfunction, DM, COPD, malignancy other than BCC, were excluded as they may affect the complete blood count and laboratory parameters. In addition, patients with low mean corpuscular volume (MCV <80 fL) in CBC analysis were excluded from the study because small red blood cells could be mistakenly counted as platelets by the analyzer.

Serological Measurements

Anti-HCV measurement of patients was made with the Anti-HCV II kit in accordance with standard procedures. The mandatory dilution measure in the test was accepted as 1:100 (for the Elecsys 2010 and Cobas e411, Roche Diagnostics GmbH, Mannheim, Germany). Anti-HCV concentration was measured using an electro-chemiluminescence immunoassay (ECLIA) (Cobas e411, Roche Diagnostics, Mannheim, Germany). All tests, including calibrations and control, were performed and interpreted according to the manufacturer's recommendations.

Calculation of Liver Fibrosis Indirect Markers

AAR (AST / ALT ratio), APRI (AST / Plt ratio index) and FIB-4 index (Age (years) x AST (U / L), which are markers that are used to indirectly predict liver fibrosis in the presence of CBC and biochemical measurements obtained from patients / [Platelet number (10^9 / L) x (ALT) 1/2 (U / L)], MPV / Plt ratio = MPV / Plt, APRI = [(person AST / AST reference upper limit) x Plt x 100] were calculated as specified in the literature (6).

Statistical Analysis

The IBM SPSS 26.0 and Modeler 18.0 (IBM Corporation, Armonk, New York, United States) programs were used in the analysis of variables. The compatibility of univariate data to normal distribution was evaluated using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used together with Monte Carlo results to compare two independent groups with each other according to the quantitative data. In the comparison of categorical variables with each other, the Pearson chi-Square test was used withExact results and the column proportions were compared with each other and expressed according to the Benjamini-Hochberg corrected p-value results. The Odds ratio was used with 95% confidence intervals to compare the risk between the two groups.In order to determine the cause-effect relationship between the categorical response variable and the explanatory variables, all the variables that were significant in the univariate analyzes were included and a logistic regression test was applied using the Backward elimination method. The Neural Network (Radial Basis) was used to find and predict the variable with the highest significance in the patient and healthy groups, considering the Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC) and accuracy rates obtained for supervised machine learning methods. Gradient descent was used for the Neural Network (Radial Basis) analysis and the optimization algorithm, Softmax was used as the hidden layer activation function and, identity was used in the output layer as the activation function. The Mini-Batch method was used for the selection of training data, of which70% was the Training set and 30% the Testing set. Quantitative variables were expressed as mean, ± SD (standard deviation), median (Percentile 25% / Percentile 75%) in tables, while categorical variables were shown as n (%). Variables were analyzed at a 95% confidence level and a p-value of less than 0.05 was considered to be significant.

RESULTS

A total of 2,887 patients of which 1,273 were anti-HCV (+) were included in our study. People with antiHCV (+) were found to be older and male-gender predominant (OR: 1.5, CI:95%, p<0.001). Total leukocyte, neutrophil, MCV and RDW levels of the patients were found to be higher than those in the control group (p<0.001). However, Hb, Lym, Plt and MPV levels were found to be lower than the control group (p<0.001). APRI, MPV / Plt R and RPR levels being hepatic damage indirect markers were found to be higher in patients with anti-HCV (+) than those in the control group (p<0.001) (Table 1).

The anti-HCV positivity rate was 1.5 times higher in men than women (Table 1). WBC, NEU, MCV and PDW counts were found to be higher in individuals with anti-HCV (+) than in the control group, while Lym, Hb, Plt and MPV counts were found to be lower (p<0.001).

The median AST value of 1,273 anti-HCV positive patients included in our study was 34 (10/5905) IU / L and the median ALT value was 27 (10/3400) IU / L. The median total bilirubin value of anti-HCV (+) patients was 0.58 (0.01 / 38.87) mg / dL and the median direct bilirubin value was determined as 0.26 (0.01 / 26.26) md / dL (Table 2). The median FIB-4 value of anti-HCV (+) patients was found to be 1.94 (0.07 / 297.41), APRI, 0.12 (0.03 / 3.75), AAR, 1.36 (0.05 / 108.82), MPV / Plt ratiom 0.037 (0.01 / 0.93), and RPR,0.05 (0.01 / 0.93) (Table 3).

DISCUSSION

Interest in ALT, AST and platelet counts and indirect markers that can be easily obtained with these parameters in the evaluation of liver damage in chronic HCV infection has recently increased. In Somalia, Mogadishu, where our study was conducted, Class I (indirect) liver damage markers are needed in conditions where Class I serum biomarkers and non-invasive NIF measurement instruments cannot be used clinically due to the lack of sufficient infrastructure and pathology units to perform liver biopsies, as a result of financial difficulties.

Therefore, non-invasive methods (NIF) are needed to evaluate liver fibrosis in chronic FlCV infection. These methods can be classified as serum markers or imaging methods (Fibroscan, MRI, Shear wave elastography) that can be used individually or combined with algorithms to obtain an accurate assessment of the fibrosis score. Hyaluronic acid (HA), laminin, fibronectin, YKL-40, procollagen type 1 carboxy terminal peptide (PICP), procollagen type lll amino-ter-

minal peptide (PIIIMP), alpha-2-macroelohulin, N-terminal propeptide of type II collagen, tissue inhibitors of matrix metalloproteinases (TIMPs), metalloproteinases (MMPs), and transforming growth factor-b1 (TGF-bl) are the direct tests for liver fibrosis (Class I). However, in routine clinical evaluation, the use of direct fibrosis markers is diffciult due to their high cost, reproducibility and their limitations as screening tests.

Table 1: Demographic and laboratory results of participants.

		Total	Control	Anti-HCV (+)	P
		(n=2887)	(n=1614)	(n=1273)	
		n (%)	n (%)	n (%)	
Gender	Female	1282 (44.4)	788 (48.8)	494 (38.8)	**<0.001** [p]
	Male	1605 (55.6)	826 (51.2)	779 (61.2)	1.5 (1.3 - 1.7)[or]
		Median (Q1 / Q3)	Median (Q1 / Q3)	Median (Q1 / Q3)	
Age		51 (32 / 67)	40 (26 / 55)	65 (53 / 73)	**<0.001** [u]
WBC		6.31 (5.14 / 7.83)	6.26 (5.19 / 7.35)	6.48 (5.04 / 8.97)	**<0.001** [u]
NEU#		3.45 (2.59 / 4.69)	3.38 (2.67 / 4.29)	3.59 (2.41 / 5.8)	**<0.001** [u]
Lym#		2.04 (1.56 / 2.55)	2.17 (1.72 / 2.61)	1.86 (1.3 / 2.44)	**<0.001** [u]
Hb (g/dL)		13.7 (12.6 / 14.8)	14.2 (13.3 / 15.1)	12.9 (11.3 / 14.1)	**<0.001** [u]
Hct (%)		40.2 (37.2 / 42.9)	41.2 (38.9 / 43.4)	38 (33.2 / 41.7)	**<0.001** [u]
MCV (pg/mL)		86.8 (83.9 / 89.8)	86.4 (84.1 / 88.9)	87.7 (83.5 / 91.2)	**<0.001** [u]
RDW (%)		13.1 (12.5 / 13.7)	12.9 (12.4 / 13.3)	13.4 (12.7 / 14.7)	**<0.001** [u]
Plt		260 (200 / 314)	279 (232 / 329)	214 (154 / 287)	**<0.001** [u]
PDW		14.1 (11.6 / 16.1)	12.2 (10.9 / 14.1)	16.1 (15.5 / 16.6)	**<0.001** [u]
MPV		9.7 (8.8 / 10.4)	10.1 (9.5 / 10.5)	8.8 (8 / 9.8)	**<0.001** [u]
APRI		0.12 (0.10 / 0.15)	0.11 (0.09 / 0.13)	0.14 (0.10 / 0.19)	**<0.001** [u]
MPV/Plt Ratio		0.037 (0.03 / 0.05)	0.036 (0.03 / 0.04)	0.042 (0.03 / 0.06)	**<0.001** [u]
RPR		0.051 (0.04 / 0.07)	0.046 (0.04 / 0.05)	0.063 (0.05 / 0.09)	**<0.001** [u]

WBC: White blood cell count, **Neu:** Neutrophil count, **Lym:** Lymphocyte cound, **Hb:** Hemoglobin value, **APRI:** Aspartate Transaminase (AST) / Platelet count ratio index, **FIB-4:** Fibrosis-4 score, **AAR:** AST/ALT ratio, **Plt:** Platelet count, **MPV:** Mean platelet volume, **RDW:** Red cell distribution, **RPR:** RDW/Plt; p Pearson chi-Square test(Exact). u Mann Whitney U test (Monte Carlo). or Odds Ratio (%95 Confidence Interval). **Q1:** Percentile 25%, **Q3:** Percentile 75%

Table 2: Laboratory results and Class II biomarker results of Anti-HCV (+) patients.

	Values (Mean+/-SD)		Minimum	Percentile 25	Median	Percentile 75	Maximum
Anti-HCV	20.45	23.41	1.01	6.59	12.76	24.00	169.30
ALT	46.30	125.40	10.00	18.00	27.00	44.00	3400.00
AST	68.36	230.48	10.00	23.00	34.00	61.00	5905.00
T. Bilirubin	1.10	2.15	0.01	0.40	0.58	0.95	38.87
D. Bilirubin	0.73	1.83	0.01	0.16	0.26	0.53	26.26
FIB-4	3.88	11.58	0.07	1.13	1.94	3.83	297.41
APRI	0.14	0.12	0.03	0.10	0.12	0.15	3.75
AAR	1.67	3.28	0.05	0.95	1.36	1.83	108.82
MPV/Plt Ratio	0.04	0.03	0.01	0.03	0.037	0.05	0.93
RPR	0.06	0.06	0.02	0.04	0.05	0.07	2.16

WBC: White blood cell count, **Neu:** Neutrophil count, **Lym:** Lymphocyte cound, **Hb:** Hemoglobin value, **APRI:** Aspartate Transaminase (AST) / Platelet count ratio index, **FIB-4:** Fibrosis-4 score, **AAR:** AST/ALT ratio, **Plt:** Platelet count, **MPV:** Mean platelet volume, **RDW:** Red cell distribution, **RPR:** RDW/Plt; p Pearson chi-Square test(Exact). u Mann Whitney U test (Monte Carlo). or Odds Ratio (%95 Confidence Interval). **Q1:** Percentile 25%, **Q3:** Percentile 75%

Table 3: Testing performance of the Class II biomarkers for Anti-HCV positivity.

Variable Importance		Sample (Holdout)	Predicted		
Independent Variable	**Normalized Importance**		**Control**	**Anti HCV positive**	**Percent Correct**
Hb	100.0%	**Training (70%)**			
MPV	94.6%	Control	958	173	84.7%
RPR	89.4%	ANTI HCV positive	158	734	82.3%
APRI	84.6%	Overall Percent	55.2%	44.8%	83.6%
MPV/Plt Ratio	79.1%	**Testing (30%)**			
Age	78.7%	Control	417	66	86.3%
Gender	16.3%	ANTI HCV positive	54	327	85.8%
		Overall Percent	54.5%	45.5%	86.1%

Neural Network (Radial Basis Function), Hidden layer activation function: Softmax, Output layer activation function: identity, Dependent Variable: Groups; Hb: Hemoglobin value, **APRI:** Aspartate Transaminase (AST) / Platelet count ratio index, **RPR:** RDW/Plt.

In our study, based on this need, we aimed to distinguish anti-HCV (+) patients from anti-HCV (-) individuals and measure the severity of liver damage using indirect liver fibrosis biomarkers in patients with anti-HCV (+).

Mean platelet volume (MPV), a parameter generally determined by complete blood count analyzers, indicates the average size of platelets and reflects the stimulation and rate of platelet production. MPV is a laboratory marker derived from complete blood count (CBC) analyzers in routine clinical practice. It is an inexpensive parameter that can be easily obtained with CBC in all patients admitted to the hospital (7). There is a also an inverse proportion between MPV and Plt. Karagoz et al. reported that MPV and RDW values were significantly higher in chronic hepatitis B patients, depending on the severity of the disease and could be used as independent predictive factors in liver fibrosis (7). Shao et al. similarly stated that Plt, PDW and P-LCR (platelet large cell ratio) values could be used to predict the severity of HCV liver damage (8). In our study, it was found that the MPV value decreased compared to that of the control group. We think that this is influenced by MPV levels, which vary inversely with the Plt score (8).

Although some studies help predict the severity of fibrosis indirectly, the use of the AAR value as a liver fibrosis biomarker has not been recommended due to low sensitivity results in recent years (9,10). Some studies indicate that it is possible to predict liver cirrhosis if AAR>1, but it has been emphasized in recent years that this rate has no significant predictive value (10-12). In our study, the AAR index was found to be 1.36 (0.05 / 108.82), similar to the results reported in the literature. APRI, which is the AST / platelet index, is a compact biomarker associated with a worsening of fibrosis and increased portal pressure, decreased thrombopoietin production by hepatocytes, increased platelet sequestration in the spleen, and decreased AST clearance. Among these markers, APRI is the most widely used and the one in which accuracy has been investigated (13,14).

Studies have shown only moderate accuracy for APRI in detecting HCV-associated fibrosis. AUROC values of APRI for the diagnosis of significant fibrosis (according to METAVIR ≥ F2), severe fibrosis (≥ F3), and cirrhosis were found to be 0.77, 0.80 and 0.83, respectively (15). FIB-4 is a non-invasive indirect liver damage marker used for the evaluation of liver fibrosis based on simple variables such as age, AST, ALT and platelet count. Sterling et al. emphasized that individuals with HCV / HIV co-infection exhibit high sensitivity in the prediction of severe liver damage through the evaluation of FIB-4 (cut-off value >1.5) and APRI (cut-off value >0.5) scores together (16). In this way, the importance of the combined use of indirect biomarkers in identifying patients who need a liver biopsy is emphasized. In our study, the median FIB-4 value of anti-HCV (+) patients was determined to be 1.94 (0.07 / 297.41), and it is striking that the number of patients above the cut-off value stated in the literature was found to be high. RDW is one of the parameters used to make the morphological classification of anemia.

Recently, markers derived or calculated from CBC indices, including RDW and / or RPR, have also been considered as independent risk factors for studying liver diseases such as HBV-related diseases (17). He et al. found that the increase in RPR and RDW in patients with chronic HCV hepatitis was associated with an increase in the severity of liver damage (18). Similar to the literature, in our study, it was found that the RDW and RPR indices in anti-HCV (+) patients were found to be significantly higher than those in the control group.

Our study has important limitations. Failure to carry out HCV-RNA measurements of the patients and the routine application of anti-HCV confirmation tests stand out as an

important health system problem due to the region where the study was conducted. In addition, the development of fibrosis and cirrhosis could not be evaluated due to the absence of liver US results and liver biopsy data. Our study is important in that it includes the anti-HCV prevalence and indirect markers of liver damage in adults in the Mogadishu region. It will be possible to reveal the severity of HCV hepatitis through studies which include biopsy and US images. We realize that our work can be regarded a pioneer study in this respect.

In conclusion, although indirect biomarkers such as MPV, MPR, RPR, FIB-4 and APRI seem to show poor performance in predicting liver fibrosis, they seem to be advantageous because they do not incur additional costs, are easy to calculate, and are reproducible through tests performed in many clinics. However, none of these measurements are liver specific, and interpretation of the results is critical as the results can often be affected by comorbid conditions.

We think that APRI, MPR, MPV / Plt ratio and FIB-4 biomarkers in particular are useful tests in terms of their predicting fibrosis and in predicting its severity in patients with anti-HCV (+) in the Somali Mogadishu Hospital located in the Sub-Saharan Africa region where our study was conducted. It is important to ensure that patients who have high indexes receive antiviral treatment through referral to liver US and, if necessary, liver biopsy in the early period.

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Author Contributions

Study Conception and Design, Acquisition of Data, Analysis and Interpretation of Data, Drafting of Manuscript, Critical Revision: Öznur Sarı

Conflicts of Interest

I have no conflicts of interest.

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Ethical Approval

This study was initiated after the approval of the local Ethics Committee of the Mogadishu Somali Turkey Recep Tayyip Erdogan Training and Research Hospital(07.08.2019 MSTH/1815).

Review Process

Extremely peer-reviewed with three reviewer and accepted.

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