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A Novel Noninvasive Index for Assessment of Liver Fibrosis and Cirrhosis in Patients with Chronic Hepatitis C Virus Infection

Mohamed Rizk Elmdams, Said Abdel Baky Gad, Mohamed Samy Farouk Gawish*
Internal Medicine Department, Faculty of medicine, Zagazeg University, Egypt
***Corresponding Author**: Mohamed Samy Farouk Gawish, **Mobile:** (+20) 01146768080,
E-mail: mohamed_gawish11@yahoo.com

ABSTRACT

Background: Liver fibrosis and cirrhosis are major causes of morbidity and mortality in chronic hepatitis C (CHC) patients.

Objective: To assess a novel non-invasive index in prediction of hepatic fibrosis and cirrhosis in chronic hepatitis c patients by using red cell distribution width to platelet ratio (RPR).

Patients and Methods: This cross-sectional study was conducted on 84 patients with hepatitis C virus in El Ahrar Teaching Hospital during the period from May 2019 to October 2019. The patients were classified into 3 groups, group (I) 26 CHC cases without fibrosis, group (II) 48 CHC cases with fibrosis, and group (III) 10 CHC cases with cirrhosis. The patients were subjected to history taking, clinical examination, laboratory investigations (CBC, liver function, kidney function, INR), and imaging modalities.

Results: There was a higher sensitivity of RPR (83.3%) in detecting fibrotic liver among CHC cases and ability of 73.4% to negative cases among truly negatives, with higher accuracy of 78.6% than other scores which had high sensitivity of 75%, 77.1% and 68.8% and specificity of 69.4%, 72.2% and 72.2% of APRI score, FIB4 and AAR respectively. While, there was a higher sensitivity of RPR (90%) in detecting cirrhotic liver among CHC cases and ability of 97.4% to detect negative cases among truly negatives, with higher accuracy of 96.4% than other scores, which had high sensitivity of 90%, 80% and 80% and specificity of 95.9%, 85.9% and 95.5% of APRI score, FIB4 and AAR respectively.

Conclusion: The progression and prognosis of chronic hepatitis C using a complete blood cell count.

Keywords: Chronic Hepatitis B (CHB), Hepatic Fibrosis, Cirrhosis.

INTRODUCTION

Hepatitis C virus (HCV) infects 130–170 million people worldwide, representing a global health problem. Approximately 12–25 % of infected patients clear the virus spontaneously. However, the majority of HCV-infected patients remains infected and may evolve to the chronic phase of the disease, characterizing a silent epidemic. The major complications of HCV infection are the progression to fibrosis, cirrhosis and hepatocellular carcinoma [(1)].

The assessment of disease progression not only provides useful information for diagnosis and therapeutic supervision judgment but also for monitoring disease. Different invasive and non-invasive methods are applied to diagnose the disease from initial to end stage (mild fibrosis to cirrhosis). Although, liver biopsy is still considered as gold standard to identify liver histological stages, an assessment of the disease development based on non-invasive clinical findings is also emerging and this may replace the need of biopsy in near future [(2)].

Noninvasive methods to measure severity of liver injury are clinically important in Egypt where advanced liver disease from HCV is common [(3)]. In addition, reliability of the biopsy to detect and measure hepatic pathology is not ideal, as the pathology is a diffuse process [(4)]. Most of the indices proposed in various studies would not be practical in Egypt and other developing countries because of the cost and unavailability of some tests.

The complete blood count (CBC) is one of the most frequently ordered laboratory tests in clinical practice. Standard CBC tests include white blood cell (WBC), red blood cell (RBC) and platelet counts as well as their morphological indices. Various studies have evaluated the performance of these hematological CBC parameters to predict disease severity and mortality risk. For example, the circulating platelet count has been proposed as a biomarker of liver fibrosis and cirrhosis [(5)]. An elevated red cell distribution width (RDW) has been reported to be associated with mortality and other severe adverse outcomes in cardiac, renal and infectious diseases, even in the general population [(6-9)]. Other studies have found an association between low hemoglobin (Hb) concentrations and mortality [(10)]. This study aimed to assess a novel non-invasive index in prediction of hepatic fibrosis and cirrhosis in chronic hepatitis c patients by using red cell distribution width to platelet ratio.

PATIENTS AND METHODS

This study included 84 CHC patients aged 48-68 years, which were classified into 3 groups 26 CHC cases without fibrosis, 48 CHC cases with fibrosis and 10 CHC cases with cirrhosis. All patients collected

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from Al-Ahrar Teaching Hospital in the period from May 2019 to October 2019.

Inclusion criteria: Patients with hepatitis C virus, males and females.

Exclusion criteria: Patients with HIV. Patients with hepatitis B virus. Patients with malignant disease. Patients with history of alcohol abuse. Patients with history of blood transfusion. Presence of other disorders or diseases that may affect hematological indices.

Ethical and patients' approval: The work has been carried in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsiniki) for studies involving humans. A written informed consent was handled from the patients to contribute in the study. **Approval for carrying out the work was received from the Departments of Internal Medicine and Clinical Biochemistry Academic Review Board , University Hospitals of Zagazig.**

Study tools and data collection:

Complete history taking. Clinical assessment was performed for all patients. Local abdominal examination with especial attention to presence of hepatomegaly or splenomegaly. Any stigmata of liver cirrhosis and/or liver cell failure (e.g.: jaundice, ascites, spider nevi ….etc.).

Laboratory investigations were done to verify eligibility of patients to be included in the study: Routine investigations: Complete blood count using automated cell counter "cell dyne" (APOTT, USA) including red blood cell distribution width (RDW), MPV and RPR.

Complete liver biochemical profile: Serum bilirubin (total and direct). Liver enzymes (AST, ALT). Serum albumin and serum creatinine on Auto Analyzer "Cobas 501" (Roche diagnostics, Switzerland). PT and INR using automated analyzer "CA1500"(Siemens, Germany). HCV Ab by ELISA technique and HCV-RNA PCR and HBsAg.

All patients were subjected to the following:

Withdrawal of venous blood sample that was distributed to the following tubes:

1) EDTA tube for complete blood count.
2) Sodium citrate tube for assay of INR.
3) Plain tube for assay of liver and kidney functions.
4) Pelvi-abdominal U/s: Ultrasound is a major screening tool for cirrhosis and its complications (Sonoscape S11 machine with a transducer of 3.5 MHz was used).
5) **Fibroscan technique:** Transient elastography (TE).

Patients lied in the dorsal decubitus position with their right arm in maximal abduction. The tip of the probe transducer was placed on the skin between the ribs at the level of the right lobe of the liver. The operator, assisted by ultrasound time-motion and Amode images provided by the system, located a portion of the liver that is at least 6 cm thick and free of large vascular structures. Once the area of measurement has been located, the operator pressed the probe button to begin the acquisition. A vibration of mild amplitude and low frequency was transmitted from the vibrator to the tissue by the transducer itself, which induces propagation of an elastic shear wave through the tissue. A pulse-echo acquisition was performed at this time to follow the propagation of the shear wave and measure its velocity, which was directly related to the liver stiffness, the harder the tissue, the faster the propagation of the shear wave. Liver stiffness measurement was expressed in kilopascals (KPa). Ten successful acquisitions were performed on each patient.

The median value was expressed as final result of the liver stiffness. The success rate is calculated as the ratio of the number of successful acquisitions to that of the total number of acquisitions and a success rate of at least 60% or the interquartile range (IQR) < 30% were considered reliable.

Statistical Analysis

Data were analyzed using IBM SPSS version 23.0 for windows (SPSS Inc., Chicago, IL, USA) and NCSS 11 for windows (NCSS LCC., Kaysville, UT, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Analysis of variance (ANOVA) F test of significance was used when comparing between more than two means. Krusskal-wallis test was used when comparing more than two means of not normally distributed data. Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters. Pearson's correlation coefficient (r) test was used for correlating continuous data. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values. Area under curve (AUC) was also calculated, criteria to qualify for AUC were as follows: 0.90 – 1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair; 0.60-0.70 = poor; and 0.50-0.6 = fail. The optimal cutoff point was established at point of maximum accuracy.

Scoring of fibrosis:

APRI defined as: 100 × {(AST/upper limit of normality)/platelet count (10^9/L)} **[11].**

FIB-4 calculated as: age (years) × AST /platelet count (109/L))×ALT½**[12].**

AST-to-ALT ratio **(AAR) [13].**

$$AAR = \frac{AST}{ALT}$$

RESULTS

Table (1): Demographic and clinical data of both studied groups

Variables	Group I (N=26)		Group II (N=48)		Group III (N=10)		F test	P-value
Age (years) **Mean ±SD** **Range**	**55.96 ± 4.6** **48 – 64**		**59.5 ± 5.1** **48 - 68**		**58 ± 2.2** **56 - 60**		**5.23**	**0.007** **S**
	N	**%**	**N**	**%**	**N**	**%**	**X^2**	**P-value**
Sex **Male** **Female**	**15** **11**	**57.7** **42.3**	**24** **24**	**50** **50**	**5** **5**	**50** **50**	0.43	0.81 NS

There was a statistically significant difference among studied groups regarding age, which was higher among fibrotic and cirrhotic groups, while all groups were matched in sex with no significant difference (Table 1).

Table (2): Difference in CBC among both studied groups

Variables	Group I (N=26)	Group II (N=48)	Group III (N=10)	F test\ KW#	P-value
Hb (mg\dl) **Mean ±SD**	**11.3 ± 1.27**	**11.2 ± 1.25**	**11.9 ± 1.74**	**1.13**	**0.33** **NS**
RBCs (10^{12}\L) **Mean ± SD**	**4.9 ± 0.57**	**4.84 ± 0.58**	**4.82 ± 0.12**	**10.3**	**0.216** **NS**
RDW (%) **Mean ± SD**	**12.5 ± 1.1**	**13.95 ± 1.8**	**17.2 ± 2.25**	**25.5**	**<0.001** **HS**
TLC (mm3) **Mean ± SD**	**6907.7 ± 618.2**	**5819.2 ± 222.6**	**6100 ± 581**	**5.06#**	**0.126** **NS**
Platelet count **Mean ± SD**	**181.1 ± 6.3**	**165.9 ± 4.4**	**117.5 ± 8.4**	**8.42**	**<0.001** **HS**
MPV (fL) **Mean ± SD**	**7.98 ± 1.81**	**9.94 ± 1.43**	**12.5 ± 1.17**	**32.8**	**<0.001** **HS**
RPR (µL) **Mean ± SD**	**0.98 ± 0.07**	**1.63 ± 0.27**	**2.42 ± 0.2**	**173.1**	**0.001** **HS**

HS: P-value < 0.001 is high significant S: P-value ≤ 0.05 is significant NS: P-value > 0.05 is not significant

This study showed a statistically significant difference among three studied groups regarding RBCs count, RDW, platelet count, mean platelet volume (MPV) and RPR. There was a statistically significant difference among cirrhosis group and the other groups regarding all parameters, there was non-significant difference among groups I and II regarding RBCs count and platelet count, while there was significant difference as regards other parameters (Table 2 and figure 1).

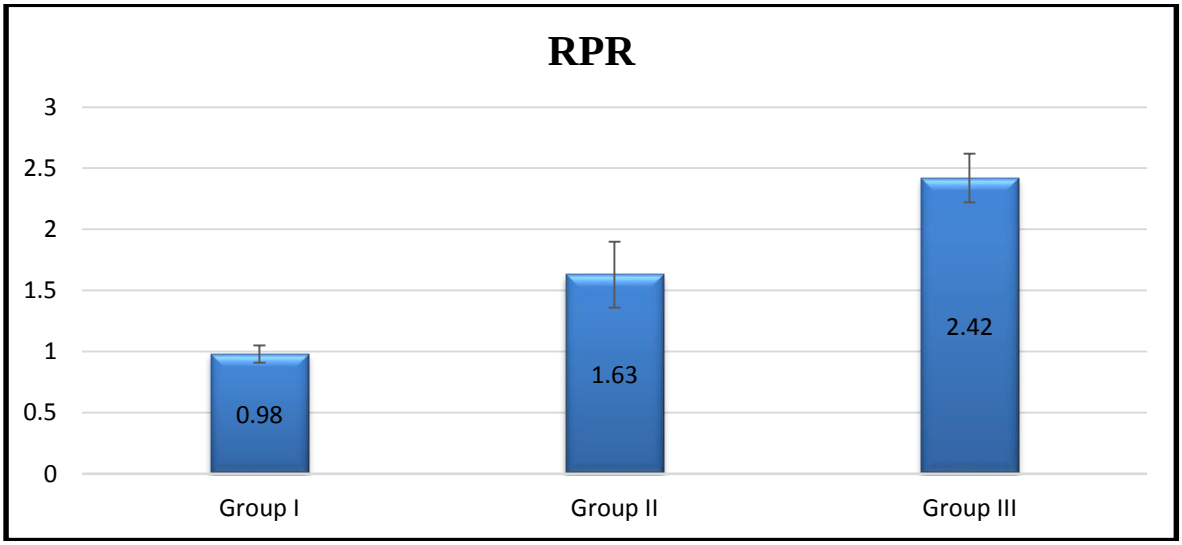

Figure (1): Difference in RPR among three studied groups.

Table (3): Difference in liver and kidney function tests among studied groups.

Variables	Group I (N=26)	Group II (N=48)	Group III (N=10)	F test\ KW#	P-value
ALT (U\L)					
Median	**15.5**	**29.3**	**68.4**	**20.1#**	**<0.001**
Mean ±SD	**22.6 ± 1.8**	**29.9 ± 1.7**	**58.8 ± 2.7**		**HS**
AST (U\L)					
Median	**26.8**	**33.7**	**46.95**	**17.8#**	**<0.001**
Mean ± SD	**27.9 ± 1.8**	**33.8 ± 5.98**	**46.95 ± 0.16**		**HS**
Billirubin					
Median	**1.15**	**1.32**	**1.5**	**9.12#**	**0.01**
Mean ± SD	**1.15 ± 0.35**	**1.37 ± 0.28**	**1.5 ± 0.11**		**S**
Albumin					**<0.001**
Mean ± SD	**4.22 ± 0.42**	**3.4 ± 0.41**	**2.3 ± 0.32**	**84.6**	**HS**
Creatinin					
Median	**0.86**	**1.3**	**1.61**	**21.6#**	**<0.001**
Mean ± SD	**0.93 ± 0.03**	**1.5 ± 0.07**	**1.61 ± 0.05**		**HS**
INR					**0.01**
Mean ± SD	**1.2 ± 0.15**	**1.3 ± 0.06**	**1.4 ± 0.01**	**4.13**	**S**

HS: P-value < 0.001 is high significant S: P-value ≤ 0.05 is significant

Table (3) showed that there were statistically significant differences among the three studied groups regarding results of liver and kidney function tests.

Table (4): Difference in diagnostic scores among studied groups.

Variables	Group I (N=26)	Group II (N=48)	Group III (N=10)	F test\ KW#	P-value
APRI score					**<0.001**
Mean ± SD	**0.26 ± 0.1**	**0.65 ± 0.22**	**1.23 ± 0.1**	**109.1**	**HS**
FIB4 score					**<0.001**
Mean ± SD	**1.31 ± 0.24**	**2.65 ± 0.61**	**4.36 ± 0.44**	**139.4**	**HS**
AAR					**<0.001**
Mean ± SD	**0.89 ± 0.204**	**2.1 ± 0.503**	**4.3 ± 0.34**	**245.6**	**HS**

HS: P-value < 0.001 is high significant S: P-value ≤ 0.05 is significant

This study showed that there were high statistically significant differences among the three studied groups regarding all diagnostic scores, which were higher among cirrhotic group (Table 4).

Table (5): Post hoc test (LSD) within the studied groups in relation to significant scores.

Variables	Mean difference Group I With	P-value	Mean difference Group II with	P-value
APRI score	Group II=-0.39 Group III=-0.97	<0.001 <0.001	Group III=-0.57	<0.001
FIB4	Group II=-1.3 Group III=-3.04	<0.001 <0.001	Group III=-1.7	<0.001
AAR	**Group II=-1.19 Group III=-3.4**	**<0.001 <0.001**	**Group III=-2.2**	**<0.001**

There were high statistically significant differences among the three studied groups regarding all diagnostic scores, which were higher among cirrhotic group followed by fibrosis group then group I (Table 5).

Figure (2) showed that all cases of group I were of grade 0 and all cases of group III were of grade 4, while 60% of group II were of grade 1 and 22.9% of grade 2, with a highly statistically significant difference among them.

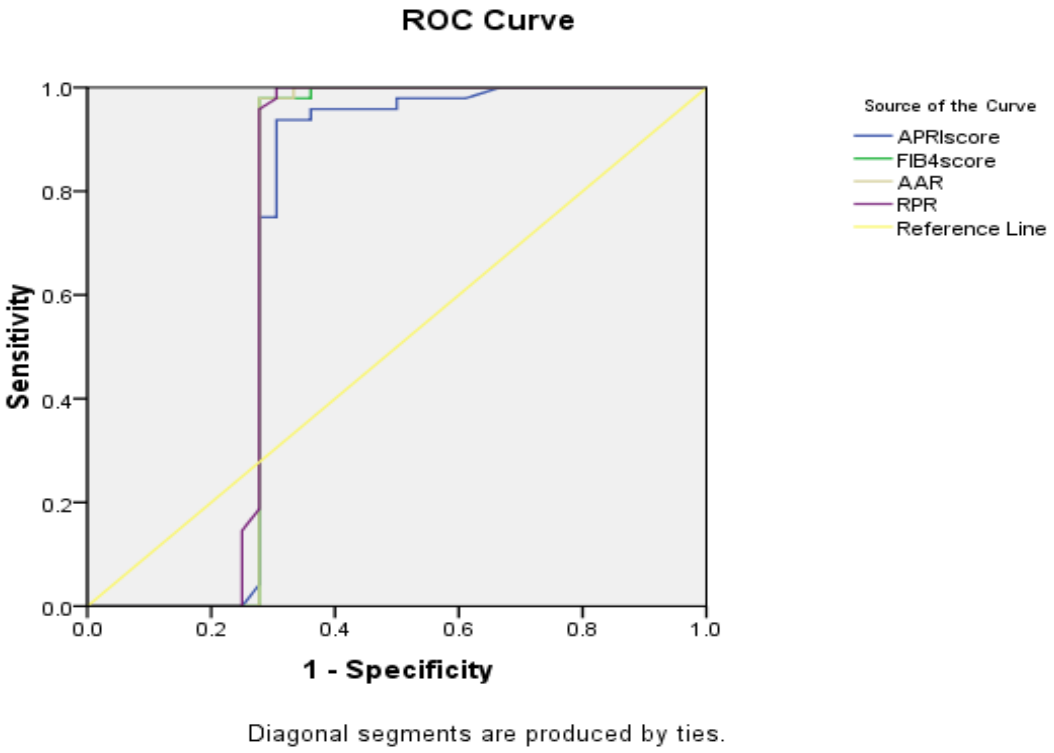

Figure (2): Receiver operating characteristics curve (ROC) of studied scores in differentiation of liver fibrosis.

Figure (3) showed a higher sensitivity of RPR (83.3%) in detecting fibrotic liver among CHC cases and ability of 73.4% to negative cases among truly negatives, with higher accuracy of 78.6% than other scores, which had high sensitivity of 75%, 77.1% and 68.8% and specificity of 69.4%, 72.2% and 72.2% of APRI score, FIB4 and AAR respectively (Figure 3).

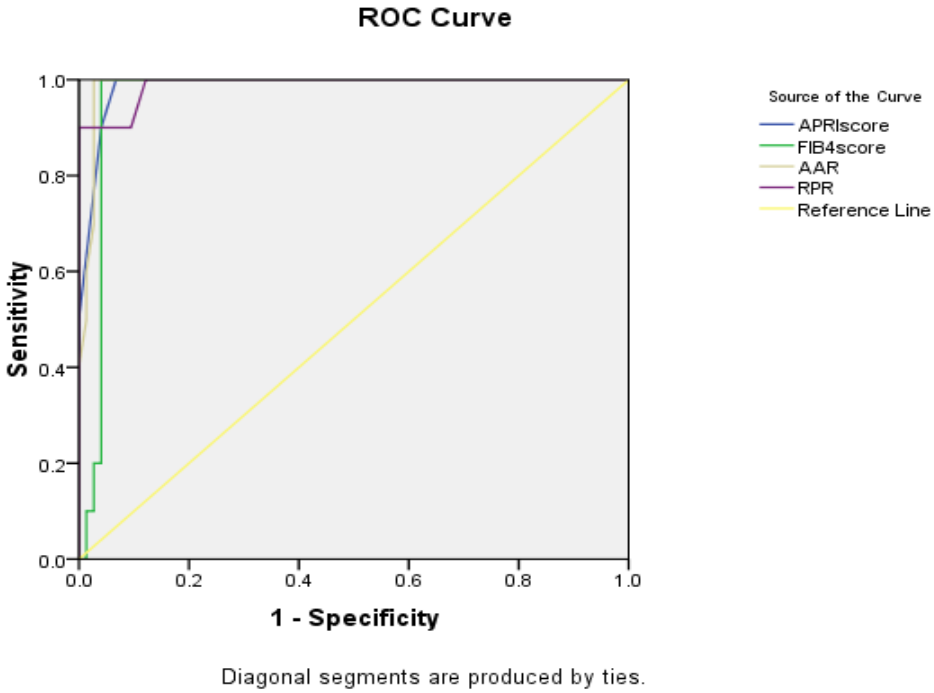

Figure (3): Receiver operating characteristics curve (ROC) of studied scores in differentiation of liver cirrhosis.

Table (6): Validity data of studied scores in differentiation of liver cirrhosis.

	Cut-off	AUC	Sensitivity	Specificity	PVP	PVN	P value	Accuracy
APRI	**1.15**	**0.986**	**90%**	**95.9%**	**75%**	**98.6%**	**<0.001**	**95.2%**
FIB4	**4.1**	**0.964**	**80%**	**85.9%**	**44.4%**	**97%**	**<0.001**	**85.7%**
AAR	**3.94**	**0.988**	**80%**	**95.5%**	**72.7%**	**97.2%**	**<0.001**	**94%**
RPR	**2**	**0.989**	**90%**	**97.4%**	**81.8%**	**98.6%**	**<0.001**	**96.4%**

This study showed higher sensitivity of RPR that was 90% in detecting cirrhotic liver among CHC cases and ability of 97.4% to detect negative cases among truly negatives with higher accuracy of 96.4% than other scores, which had high sensitivity of 90%, 80% and 80% and specificity of 95.9%, 85.9% and 95.5% of APRI score, FIB4 and AAR respectively (Table 6).

Table (7): Correlation between severities of liver fibrosis with clinical data of the studied cases.

	Severity of liver fibrosis		
	r	P	
APRI score	**0.654**	**<0.001**	**HS**
RPR	**0.838**	**<0.001**	**HS**
FIB4	**0.564**	**<0.001**	**HS**
AAR	**0.751**	**<0.001**	**HS**
Hb	0.096	0.353	NS
RDW	**0.620**	**<0.001**	**HS**
Platelet count	**-0.385**	**<0.001**	**HS**
TLC	**-0.244**	**0.03**	**S**
MPV	**0.666**	**<0.001**	**HS**

Table (7) showed a high statistically significant positive correlation between liver fibrosis and all diagnostic scores assessed APRI, RPR, FIB4, AAR, RDW and MPV, while there was significant negative correlation with platelet count and TLC.

DISCUSSION

In the present study, there was a statistically significant difference between the studied groups regarding age. Patients in group II and III were older than patients in group I. The mean age of patients in group I, II and III were 55, 59 and 58 years old ranging from 48 to 68 years old. This reflect that patients were infected during their active phases of life being subjected to the different risk factors of HCV infection. This is in agreement with **Mabrouk *et al.*** [(14)] who reported a mean age of 42 years old. In addition, **Esmat *et al.*** [(15)] reported that older age, but not gender, was associated with the stage of fibrosis and cirrhosis.

In this work, as regards sex, no statistically significant difference was present between the studied groups. This is in agreement with **Schiavon *et al.*** [(16)] who reported that there was no statistically significant difference between the studied groups as regards gender.

Also, in the current study there was 44 males (52.4%) and 40 females (47.6%), the male predominance highlighted the high exposure rate and the percentage of adult males seeking medical advice. **Gad *et al.*** [(17)], **Mabrouk *et al.*** [(14)] and **Chen and Morgan** [(18)] reported a similar male predominance. These results probably explained by the characteristics of the blood donor population who are presumably healthy adult males who seek medical assistance after being diagnosed in blood banks.

In this work, there were statistically significant differences present in baseline laboratory data as regards serum albumin that was higher in group I than in groups II and III and INR that was higher in groups II and III than in group I**.**

In the present study, RDW was increased in cirrhosis and fibrosis than in cases without fibrosis. The RDW, an indicator of the variability of the circulating RBC size, is often used to diagnose different types of anemia. Recent studies have reported that a higher RDW is associated with a higher mortality risk in various patient populations. A prospective study by **Patel *et al.*** [(19)] showed that the RDW was a strong predictor of mortality in middle-aged and older adults. Another study by **Lou *et al.*** [(20)] reported that increased RDW values were associated with disease severity in patients with hepatitis B.

High Statistically significant difference was present in platelet count that was higher in group 1 than in groups II and III**.** This difference may be due to decreased production of thrombopoietin by hepatocytes that could explain the reduced platelet production, which is associated with fibrosis and cirrhosis progression [(15)]**.** **Chen and Morgan** [(18)] found that thrombocytopenia has been a well-known predictor of severe liver fibrosis. The platelet count has been used in the most predictive models for liver fibrosis and cirrhosis. The development of liver fibrosis is considered to be a complex trait. The role of platelets in the progression of fibrosis is not well understood. Recent findings have revealed a potentially beneficial role of platelets, in which they have been found to alleviate liver fibrosis through the decreased expression of the principal profibrogenic cytokine TGF-b and the increased expression of matrix metalloproteinases [(21)].

In this work, there was statistically significant difference at MPV count between groups I, II and III. It was higher in fibrosis and cirrhosis. This came in agreement with two other retrospective studies revealed that MPV was increased in chronic hepatitis C patients with advanced fibrosis [(22, 23)]**.** Although increasing evidence highlights the prognostic value of individual CBC parameters [(24, 25)]. However, to our knowledge, our study is the first in Egypt to report the relationship between RDW and the stage of liver fibrosis and cirrhosis. Moreover, few studies have combined the RDW and platelet count, the two strongest predictors, to identify CHC patients with significant fibrosis or cirrhosis. Our study addressed this gap and found that the RDW and the RDW to platelet ratio in particular could predict the risk of significant liver fibrosis and cirrhosis.

This study showed that there was statistically significant difference as regards ALT (P = 0.001) and AST (P = 0.002) between patients with significant cirrhosis and patients without fibrosis. This is consistent with **Schiavon *et al.*** [(16)] who have reported a statistically significant difference in ALT and AST level (P = 0.002) between the studied groups. This was explained that serum ALT is released from liver tissue into the circulation in proportion to the degree of hepatocellular damage due to viral infections and toxic substances and

it is thought to be one of the most and important drive for hepatic injury [26]. However, **Fontana and Lok** [26] claimed that despite the fact that ALT levels reflect liver injury, the correlation between ALT levels and the necro-inflammatory and fibrosis scores is poor. Also, **Kim *et al.*** [27] and **Manns *et al.*** [28] found that ALT enzymatic activity may not always reflect the degree of hepatic damage as about 26% of the patients have persistently normal ALT levels but have a histological score greater than A1F1, as liver injury may occur through apoptosis.

In our study, APRI score showed significant results in differentiating liver fibrosis and cirrhosis ($P < 0.001$). This could be explained as this index depends on the increase of AST levels and the decrease in the platelets levels that occur in fibrosis and cirrhosis. APRI score was reported to be an easy, good and well validated predictor of hepatic fibrosis in patients with chronic hepatitis C. Potentially, it can be used to decrease the requirements for liver biopsies .The real strength of such an index is that it is based on blood tests that are routinely performed in patients with liver disease with no need for additional blood sampling [29]. In the present study, the sensitivity of APRI score was 75% in detecting fibrotic liver among CHC cases and ability of 69.4% to negative cases among truly negatives, with accuracy of 72.6%. For cirrhosis, sensitivity was 90%, specificity 95.9% and accuracy 95.2%. This is to some extent consistent with **Sebastiani** [30] who found that APRI performance is variable among the studies on hepatitis C with sensitivity ranged between 41% and 91%, specificity between 47% and 95% and accuracy between 60% and 65.8% for significant fibrosis. For cirrhosis, sensitivity ranged between 38.4% and 82.7%, specificity between 86.7% and 93% and accuracy between 60% and 88.4%. He also stated that APRI differentiate between significant fibrosis and cirrhosis but in approximately 50% of the cases results could not be differentiated.

In another study by **Saitou and his colleagues** [31], they found that measurements of aspartate aminotransferase (AST) to platelet ratio index, has been assessed as substitute for liver biopsy, but this method did not reflect the mechanism of liver fibrosis directly, and did not relate to the efficacy of IFN treatment in patients with HCV-associated liver disease.

In the present study, there was significant correlation between fibrosis and RDW and negative correlation with platelets. These come in agreement with **Chen and Morgan** [18] whose study was on 603 patients with CHB. They found that RDW was correlated with significant fibrosis and cirrhosis, whereas platelets were negatively correlated with significant fibrosis and cirrhosis. In addition, **Sitia *et al.*** [32] found that a negative correlation exists between liver fibrosis progression and platelets. Platelets contribute to the inflammatory reaction after liver injury in their study on a mouse model of CHB.

In the present study, there was no significant correlation between fibrosis and Hb. This comes in disagreement with some studies, which found a negative correlation between Hb and fibrosis and cirrhosis. This difference may be because our patients took treatment for anemia [18].

In the current study, A ROC curve analysis was applied to estimate the predictive values of the RPR. Meanwhile, the RPR was compared to three pre-existing noninvasive indices including the AAR, APRI and FIB-4. The RPR based on CBC parameters exhibited excellent performance in the prediction of significant fibrosis and cirrhosis. The area under the ROC curve (AUCs) of all four models was analyzed for predicting significant fibrosis and cirrhosis in the studied patients. The AUCs of the RPR, APRI, FIB-4 and AAR, were 0.726, 0.704, 0.720 and 0.721 respectively in the prediction of significant fibrosis. The AUCs of the RPR, APRI, FIB-4 and AAR were 0.989, 0.986, 0.964 and 0.988 respectively in the prediction of cirrhosis. The RPR exhibited a higher AUC in the prediction of significant fibrosis compared to the APRI, FIB-4 and AAR and in the prediction of cirrhosis compared to the APRI, FIB-4 and AAR. This comes in agreement with **Chen and Morgan** [18] who found that the AUCs of the RPR, APRI, AAR and FIB-4 were 0.825, 0.740, 0.586 and 0.795, respectively, in the prediction of significant fibrosis. The AUCs of the RPR, APRI, AAR and FIB-4 were 0.884, 0.849, 0.734 and 0.857, respectively, in the prediction of cirrhosis. The RPR exhibited a significantly higher AUC in the prediction of significant fibrosis compared to the APRI and AAR ($p = 0.05$) and in the prediction of cirrhosis compared to the AAR ($p = 0.05$).

Other models, such as the FIB-4, FibroTest-ActiTest and FibroScan (all based on chronic hepatitis C patients), were applicable to patients with CHC and CHB in some investigations but were limited by the requirement of complicated calculations or expensive instruments [27, 33, 34, 35]. The RPR requires only 2 common CBC parameters and is the simplest, cheapest and most easily calculated noninvasive method with a relatively high accuracy.

CONCLUSION

Two common hematological parameters, the RDW and platelet count, provided the greatest predictive value of liver fibrosis. The RPR, an inexpensive and easily calculated index, can predict significant fibrosis and cirrhosis in CHC patients with relatively high accuracy, potentially reducing unnecessary liver biopsies.

REFERENCES

1. **de Souza-Cruz S, Victória M, Tarragô A *et al.* (2016):** Liver and blood cytokine microenvironment in HCV patients is associated to liver fibrosis score: a proinflammatory cytokine ensemble orchestrated by TNF and tuned by IL-10. BMC Microbiol., 16: 3-6.
2. **Ahmad S, Ijaz B, Gull S *et al.* (2011):** A brief review on molecular, genetic and imaging techniques for HCV fibrosis evaluation. Virology Journal, 8: 53-8.

3. **Strickland G (2006):** Liver disease in Egypt: Hepatitis C superseded schistosomiasis as a result of iatrogenic and biological factors. Hepatol., 43: 915-922.
4. **Afdhal N, Nunes D (2004):** Evaluation of liver fibrosis: a concise review. Am J Gastroenterol., 99: 1160-1174.
5. **5-Pradella P, Bonetto S, Turchetto S *et al.* (2011):** Plateletproduction and destruction in liver cirrhosis. Journal of Hepatology, 54: 894-900.
6. **Bojakowski K, Dzabic M, Kurzejamska E *et al.* (2012):** A high red blood cell distribution width predicts failure of arteriovenous fistula. PloS One, 7: 36482-8.
7. **Horne B (2012):** A changing focus on the red cell distribution width: why does it predict mortality and other adverse medical outcomes? Cardiology, 122: 213–215.
8. **Chen P, Sung F, Chien K *et al.* (2010):** Red blood cell distribution width and risk of cardiovascular events and mortality in a community cohort in Taiwan. American Journal of Epidemiology, 171: 214–220.
9. **Patel K, Gordon S, Jacobson I *et al.* (2004):** Evaluation of a panel of non invasive serum markers to differentiate mild from moderate-to-advanced liver fibrosis in chronic hepatitis C patients. J Hepatol., 41: 935-942.
10. **Anand I, McMurray J, Whitmore J *et al.* (2004):** Anemia and its relationship to clinical outcome in heart failure. Circulation, 110: 149– 154.
11. **Wai C, Greenson J, Fontana R *et al.* (2003):** A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology, 38: 518–526.
12. **Vallet-Pichard A, Mallet V, Nalpas B *et al.* (2007):** FIB-4:aninexpensiveand accurate marker of fibrosis in HCV infection, A comparison with liver biopsy and fibrotest. Hepatology, 46: 32-36.
13. **Giannini E, Risso D, Botta F *et al.* (2003):** Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virusrelated chronic liver disease. Archives of Internal Medicine, 163: 218–224.
14. **Mabrouk M, El-Raziky M, Zayed N *et al.* (2013):** Clinical, biochemical and pathological profiles of 5464 Egyptian chronic hepatitis C- infected patients. Hepatogastroenterology, 60 (127): 1731-1735.
15. **Lackner C, Struber G, Liegl B *et al.* (2005):** Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. Hepato., 41: 1376-1382.
16. **Schiavon L, Narciso-Schiavon J, Carvalho-Filho R *et al.* (2007):** Simple Blood Tests as Noninvasive Markers of Liver Fibrosis in Hemodialysis Patients with Chronic Hepatitis C Virus Infection, Hepatology, 47: 37-45.
17. **Gad R, Males S, El-Makhzangy H *et al.* (2008):** Predictors of a sustained virological response in patients with genotype 4 chronic hepatitis C. Liver Int., 28 (8): 1112-1119.
18. **Chen S, Morgan T (2006):** The natural history of hepatitis C virus (HCV) infection. International Journal of Medical Sciences, 3: 47-53.
19. **Patel K, Ferrucci L, Ershler W *et al.* (2009):** Red blood cell distribution width and the risk of death in middle-aged and older adults. Archives of Internal Medicine, 169: 515–523.
20. **Lou Y, Wang M, Mao W (2012):** Clinical usefulness of measuring red blood cell distribution width in patients with hepatitis B. PloS One, 7 (5): 37644-9.
21. **Knight V, Tchongue J, Lourensz D *et al.* (2012):** Protease activated receptor 2 promotes experimental liver fibrosis in mice and activates human hepatic stellate cells. Hepatology, 55: 879–887.
22. **Purnak T, Olmez S, Torun S *et al.* (2012):** Mean platelet volume is increased in chronic hepatitis C patients with advanced fibrosis. Clin Res Hepatol Gastroenterol., 37 (1): 41-6.
23. **Ekiz F, Yuksel O, Kocak E *et al.* (2011):** Mean platelet volume as a fibrosis marker in patients with chronic hepatitis B. Journal of Clinical Laboratory Analysis, 25: 162–165.
24. **Uyarel H, Ergelen M, Cicek G *et al.* (2011):** Red cell distribution width as a novel prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. Coronary Artery Disease, 22: 138– 144.
25. **Dabbah S, Hammerman H, Markiewicz W *et al.* (2010):** Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. The American Journal of Cardiology, 105: 312–317.
26. **Fontana R, Lok A (2002):** Noninvasive monitoring of patients with chronic hepatitis C. Hepatol., 36: 57-64.
27. **Kim H, Oh S, Kim D *et al.* (2009):** Abundance of immunologically active alanine aminotransferase in sera of liver cirrhosis and hepatocellular carcinoma patients. Clin Chem., 55: 1022-1025
28. **Manns M, Wedemeyer H, Wiegand J *et al.* (2009):** Handbuch hepatitis C: Diagnostik, verlauf, therapie. 3rd ed. Bremen: Uni-Med Verlag AG, Pp: 46-54. https://www.amazon.co. uk/Handbuch-Hepatitis-Diagnostik-Verlauf-Therapie/dp/383742099X
29. **Snyder N, Gajula L, Xiao S *et al.* (2006):** APRI: an easy and validated predictor of hepatic fibrosis in chronic hepatitis C. J Clin Gastroenterol., 40: 535-542.
30. **Sebastiani G (2009):** Non-invasive assessment of liver fibrosis in chronic liver diseases: implementation in clinical practice and decisional algorithms. World J Gastroenterol., 15: 2190-2203.
31. **Saitou Y, Shiraki K, Yamanaka Y *et al.* (2005):** Noninvasive estimation of liver fibrosis and response to interferon Therapy by a serum fibrogenesis marker, YKL-40, in patients with HCV-associated liver disease. World J Gastroenterol., 11: 476-481.
32. **Sitia G, Aiolfi R, Di Lucia P *et al.* (2012):** Antiplatelet therapy prevents hepatocellular carcinoma and improves survival in a mouse model of chronic hepatitis B. Proceedings of the National Academy of Sciences of the United States of America, 109: 2165–2172.
33. **Mallet V, Dhalluin-Venier V, Roussin C *et al.* (2009):** The accuracy of the FIB-4 index for the diagnosis of mild fibrosis in chronic hepatitis B. Alimentary Pharmacology & Therapeutics, 29: 409–415.
34. **Wong G, Wong V, Choi P *et al.* (2008):** Assessment of fibrosis by transient elastography compared with liver biopsy and morphometry in chronic liver diseases. Clinical Gastroenterology and Hepatology, 6: 1027–1035.
35. **Poynard T, Zoulim F, Ratziu V *et al.* (2005):** Longitudinal assessment of histology surrogate markers (FibroTest-ActiTest) during lamivudine therapy in patients with chronic hepatitis B infection. The American Journal of Gastroenterology, 100: 1970–1980.