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Red Cell Distribution Width to Platelet Ratio: A Novel Noninvasive Index for Predicting Hepatic Fibrosis and Cirrhosis in Chronic Hepatitis C

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Abstract

Background:*Liver fibrosis and cirrhosis are major causes of morbidity and mortality in chronic hepatitis C (CHC) patients. The aim was 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).****Methods:****This study included 84 CHC patients 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 from Al-Ahrar Teaching hospital and subjected to full clinical history, clinical examination and Complete blood picture were measured.****Results:****There was a statistically significant difference among three studied groups regarding RPR. There was a higher sensitivity of RPR (83.3%) in detecting fibrotic liver among CHC cases with higher accuracy of 78.6% There was a higher sensitivity of RPR (90%) in detecting cirrhotic liver among CHC cases with higher accuracy of 96.4% Also, there was a high statistically significant positive correlation between liver fibrosis and all diagnostic scores assessed, APRI, RPR, FIB4 and AAR, while there was significant negative correlation with RDW, platelet count, TLC and MPV.****Conclusion:*** *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.*

Key words: *hepatic fibrosis- cirrhosis - chronic hepatitis c- RPR-Diagnosis*

I. 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)].

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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 indexes proposed in various studies would not be practical in Egypt and other developing countries because of 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)]. Other studies have found an association between low hemoglobin (Hb) concentrations and mortality [(7)].

The study aimed toassess 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.

II. Patients and Methods

(I) Patients:

This Cross-sectional study was carried out at viral hepatitis unit and hepatology department in El Ahrar Teaching Hospital and included 84 patients with hepatitis C virusduring the period from May 2019 to October 2019. Consent was obtained from each patient and approval of the ethical committee was obtained.

They were divided into three groups:

- **Group I: 26 CHC cases without fibrosis** included 15 males and 11 females aged (48 - 64) years with mean ages 55.96 ± 4.6.
- **Group II: 48 CHC cases with fibrosis** included 24 males and 24 females aged (48 - 68) years with mean ages 59.5 ± 5.1.
- **Group III: 10 CHC cases with cirrhosis** included 5 males and 5 females aged (56 - 60) years with mean ages 58 ± 2.2.

Inclusion criteria

1. Patients with hepatitis C virus.
2. Male and female

Exclusion criteria

1. Patients with HIV
2. Patients with hepatitis B virus
3. Patients with malignant disease.
4. Patients with history of alcohol abuse.
5. Patients with history of blood transfusion
6. Presence of other disorders or diseases that may affect hematological indices

(II) Methods:

All patients selected in the study were subjected to the following:

1- **History taking.**

2- **Full clinical examination.**

3- **Local abdominal examination** with especial attentionto:

- Presence of hepatomegaly orsplenomegaly.
- Any stigmata of liver cirrhosis and/or liver cell failure (e.g.: jaundice, ascites, spider nevi….etc.).

4- **Routine laboratory investigation** which include the following:

- Complete Blood Count using automated cell counter "cell dyne" (APOTT, USA) including RDW, MPV and RPR.
- Serum bilirubin, ALT, AST, 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.
- HBsAg

Sampling:

All patients were subjected for the following:

Withdrawal of venous blood sample that was divided in 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.

5- **Pelvi - abdominal U/s:**

6- Fibroscantechnique:

Statistical Analysis

Data were analyzed using IBM SPSS 23.0 for windows (SPSS Inc., Chicago, IL, USA) and NCSS 11for windows (NCSS LCC., Kaysville, UT, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- 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.
- **ROC curve were done:**
- Probability (P-value): P-value <0.05 was considered significant, P-value <0.001 was considered as highly significant and P-value >0.05 was considered insignificant.

III. Results:

This table shows that 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)**.

This table shows a statistically significant difference among three studied groups regarding RBCs count, RDW, platelet count, MPV and RPR **(Table 2)**.

This table shows that there was a statistically significant difference among cirrhosis group and the other groups regarding all significant parameters, there was no significant difference among both group I and II regarding RBCs count and platelet count, but significant difference as regard other parameters **(Table 3)**.

This table shows a high statistically significant difference among three studied groups regarding all diagnostic scores, which was higher among cirrhotic group **(Table 4)**.

This table shows that there was a high statistically significant difference among three studied groups regarding all diagnostic scores which was higher among cirrhotic group followed by fibrosis group then group I **(Table 5)**.

This table shows 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 high accuracy of 78.6%**(Table 6)**.

This table shows 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 high accuracy of 96.4% **(Table 7)**.

This table shows 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 **(Table 8)**.

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	55.96 ± 4.6		59.5 ± 5.1		58 ± 2.2		5.23	0.007 S
Range	48 – 64		48 - 68		56 - 60			
	N	**%**	**N**	**%**	**N**	**%**	**X^2**	**P-value**
Sex								
Male	15	57.7	24	50	5	50	0.43	0.81
Female	11	42.3	24	50	5	50		NS

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
Range	9.8 – 13.4	9.6-15	10.2-13.5		NS
RBCs (10^{12}\L)					
Mean ± SD	4.9 ± 0.57	4.84 ± 0.58	4.82 ± 0.12	10.3	0.216
Range	3.2 – 5.3	3.1 - 5.4	4.7 - 5.1		NS
RDW (%)					

Mean ± SD	12.5 ± 1.1	13.95 ± 1.8	17.2 ± 2.25	25.5	<0.001
Range	11.4 – 15.2	10.5 – 17.6	11.8 - 18		HS
TLC					
Mean ± SD	6907.7 ± 2618.2	5819.2 ± 2022.6	6100 ± 1581	5.06#	0.126
Range	3700 - 10400	3800 - 11000	4600 – 7600		NS
Platelet count					
Mean ± SD	181.1 ± 46.3	165.9 ± 42.4	117.5 ± 18.4	8.42	<0.001
Range	120 - 300	95 - 260	100 – 135		HS
MPV (fL)					
Mean ± SD	7.98 ± 1.81	9.94 ± 1.43	12.5 ± 1.17	32.8	<0.001
Range	6.5 – 11.8	7.3 – 12.4	9.6 – 13.8		HS
RPR					
Mean ± SD	0.98 ± 0.07	1.63 ± 0.27	2.42 ± 0.2	173.1	0.001
Range	0.89 – 1.19	1.11 – 2.04	1.99 – 2.66		HS

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

NS: P-value>0.05 is not significant

Table (3): Post hoc test (LSD) within the studied groups in relation to significant CBC parameters.

Variables	**Mean difference Group I With**	**P value**	**Mean difference Group II with**	**P value**
RBCs (10^{12}\L)	Group II=0.204 Group III=-0.75	0.128 <0.001	Group III=-0.95	<0.001
RDW (%)	Group II=-1.5 Group III=-4.7	<0.001 <0.001	Group III=-3.2	<0.001
Platelet count	Group II=15.2	0.139	Group III=48.05	0.001

	Group III=63.5	<0.001		
MPV	Group II=-1.95 Group III=-4.48	<0.001 <0.001	Group III=-2.5	<0.001
RPR	Group II=-0.65 Group III=-1.44	<0.001 <0.001	Group III=-0.79	<0.001

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					
Mean ±SD	0.26 ± 0.1	0.65 ± 0.22	1.23 ± 0.1	109.1	<0.001
Range	0.09 – 0.46	0.25 – 1.12	1.12 - 1.44		HS
FIB4 score					
Mean ± SD	1.31 ± 0.24	2.65 ± 0.61	4.36 ± 0.44	139.4	<0.001
Range	0.93 – 1.77	1.65 – 3.59	3.99 – 5.22		HS
AAR					
Mean ± SD	0.89 ± 0.204	2.1 ± 0.503	4.3 ± 0.34	245.6	<0.001
Range	0.45 – 1.27	1.18 – 3.35	3.88 - 4.67		HS

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

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	<0.001	Group III=-0.57	<0.001

	Group III=-0.97	<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

Table (6): RPR in differentiation of liver fibrosis.

	Cut-off	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**P value**	**Accuracy**
RPR	**1.34**	**0.726**	**83.3%**	**73.4%**	**80%**	**76.5%**	**<0.001**	**78.6%**

Table (7): RPR in differentiation of liver cirrhosis.

	Cut-off	**AUC**	**Sensitivity**	**Specificity**	**PVP**	**PVN**	**P value**	**Accuracy**
RPR	**2**	**0.989**	**90%**	**97.4%**	**81.8%**	**98.6%**	**<0.001**	**96.4%**

Table (8): Correlation between severity 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**

IV. 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 group I. The mean age of patients in group I, II and III were 55, 59 and 58years old ranging from 48 to 68 years old reflect that patients were infected during their active phases of life being subjected to the different risk factors of HCV infection. This result was reported by***Mabrouk et al.,*** [8]who reported mean age of 42 years old.

In this work, as regards sex no statistically significant difference was present between the studied groups. This was in agreement with ***Schiavon et al.*** [9] who reported that there was no statistically significant difference between the studied groups as regard 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. A similar male predominance was reported by ***Gad et al.,*** [10]. 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 was statistically significant difference was present in baseline laboratory data as regards serum albumin that was higher in group I than group II and III and INR that was higher in group II and III than group I**.**

In the present study, RDW was increased in cirrhosis and fibrosis than 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.** [11] showed that the RDW was a strong predictor of mortality in middle-aged and older adults. Another study by **Lou et al.** [12] reported that increased RDW values were associated with disease severity in patients with hepatitis B.

A prospective, multicenter study suggested that an elevated RDW might indicate inflammatory stress and impaired iron mobilization [13]. Indeed, inflammation and iron overload play key roles in mediating the processes associated with hepatic fibrosis [14]. Richard G Ruddell et al demonstrated a role for ferritin, an indicator of body iron stores, in regulating the expression of proinflammatory cytokines associated with hepatic fibrogenesis[15]. Furthermore, inflammatory cytokines may increase the heterogeneity of erythrocyte maturation and impairment, characterized by an elevated RDW.

High Statistically significant difference was present in platelet count that was higher in group 1 than group 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 ***(16)*****.**

Chen et al. (17) 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**(18)**.

Platelets thus appear to have a dual role in liver fibrogenesis and regeneration **(19).**

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 other retrospective study revealed that the mean platelet volume (MPV) was increased in chronic hepatitis C patients with advanced fibrosis **(20).**

Although increasing evidence highlights the prognostic value of individual CBC parameters **(21)**, 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.

In our study APRI score showed significant results in differentiating liver fibrosis and cirrhosis ($P<0.001$). This could be explained as this Index depend 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***(22)*****.**

In the present study there was significant correlation between fibrosis and RDW and negative correlation with platelets.

This came in agreement with **Chen et al. (17)**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.

Also,**Sitia et al. (23)**founda 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 came in disagreement with who found negative correlation between Hb and fibrosis and cirrhosis. This difference may be because our patients took treatment for anemia.

In the current study, A ROC curve analysis was applied to estimate the predictive values of the RPR. The RPR based on CBC parameters exhibited excellent performance in the prediction of significant fibrosis and cirrhosis. The AUCs of all four models was analyzed for predicting significant fibrosis and cirrhosis in the studied patients. The AUCs of the RPR, were 0.726, in the prediction of significant fibrosis. The AUCs of the RPR, were 0.989, in the prediction of cirrhosis. The RPR exhibited a higher AUC in the prediction of significant fibrosis and in the prediction of cirrhosis.

This came in agreement with **Chen et al.** [17]who found that the AUCs of the RPR, were 0.825, 0, in the prediction of significant fibrosis. The AUCs of the RPR, were 0.884, in the prediction of cirrhosis.

The RPR requires only 2 common CBC parameters and is the simplest, cheapest and most easily calculated noninvasive method with a relatively high accuracy.

V. Conclusion:

The present study provided important insights into the progression and prognosis of chronic hepatitis C using a complete blood cell count. 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.

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