Predictive Value of Red Cell Volume Distribution Width-to-Platelet Ratio in Staging Liver Fibrosis in Chronic HCV-Infected Patients

Ali Saad Nada[1], Nashwa Shebl[1], Ahmed Ragab El-Gazzarah[2], Warda Othman[1]

[1] *Department of Hepato-Gastroenterology, National Liver Institute, Menoufia University, Egypt.*

[2]*Department of Tropical Medicine department, Faculty of medicine, Menoufia University. Egypt.*

Corresponding Author
Ahmed Ragab El-Gazzarah

Mobile:
01009525523–
01270736429

E mail:
aragab0@gmail.com

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Background and study aim: The gold standard investigation to stage hepatic cirrhosis is liver biopsy. Being invasive with several major and minor procedure-related complications, liver biopsy is not universally-applied in all the indicated population. In addition to observer-related variations and sampling errors, the need for alternatives to liver biopsy has emerged including several lab-based indices of those; red cell volume distribution width-to-platelet ratio (RPR) have been postulated in some studies. The aim of this article is to study the diagnostic performance of RPR in staging liver cirrhosis in HCV-infected patients.

Patients and Methods: 236 patients who had underwent liver biopsy for IFN-based therapy were included in the present study according to pre-defined inclusion and exclusion criteria. They were classified into 4 groups according to the stage of cirrhosis reported by the liver biopsy. Laboratory data, including CBC and biochemical studies, RPR, APRI score and FIB-4 were tabulated for statistical analysis.

Results: The AUROCs values for RPR were 0.795, 0.811 and 0.886 for F2, F3 and F4 stage of cirrhosis respectively which were consistently higher than those of APRI (0.680, 0.754 and 0.746 for F2, F3 and F4 stages respectively) and FIB-4 (0.653, 0.765 and 0.810 for F2, F3 and F4 stages respectively). RPR was significantly-correlated with APRI ($P<0.002$), and FIB-4 ($P<0.001$) for the prediction of F3 stage of cirrhosis, and F4 stage of cirrhosis ($P<0.001$ & $P=0.03$ with APRI & FIB-4 respectively).

Conclusion: RPR can be a promising, inexpensive non-invasive tool for the prediction of the stage of hepatic cirrhosis in patients with HCV.

INTRODUCTION

HCV was discovered in 1989 and since then, it has been recognized as a major cause for chronic liver diseases worldwide accounting for more than 50% of infected cases **[1]**.

The WHO reported that about 71 million people were HCV-infected in 2015, accounting for 1% of the total population. Its prevalence is not homogenously distributed worldwide, with a general prevalence ranging 0.5-6.5% worldwide. In south-east Asia and in eastern Mediterranean regions it reaches 2.3% **[2]**.Egypt had the highest prevalence of HCV infection, and 92.5% of HCV infections belong to genotype 4, 3.6% of infections belonging to genotype 1, 3.9% of infections belonging to other genotypes **[3]**.

The gold standard investigation to stage hepatic cirrhosis is liver biopsy. Being invasive with several major and minor procedure-related complications, liver biopsy is not universally-

applicable in all the indicated population. In addition, a significant fraction of observer-related variations and sampling errors exists **[4]**.

Furthermore, repeated biopsy is not applicable to monitor the fibrotic regression in the era of DAAs. As a result, several non-invasive alternatives have been studied and proved reasonable usefulness for estimating the stage of hepatocirrhosis of different etiologies. These methods included transient elastography (TE), APRI and FIB-4 scores. Being non-invasive, highly accurate, TE has proved to be a trusted alternative to liver biopsy. However, due to its limited availability (mostly available in tertiary healthcare centers), many of biopsy-indicated patients won't be able to make use of its benefits **[5]**.

Red cell distribution width (RDW) is reported routinely by clinical labs as a part of the regular complete blood count. It is used to diagnose the etiology of anemia. It is calculated as the quotient of the standard deviation of the RBC size to the mean corpuscular volume, and it reflects the variation of heterogeneity in the volume of RBCs. Increased RDW indicates dysfunctional erythropoiesis, shortened RBC lifespan, or premature release of reticulocytes. Traditionally, RDW has been used in diagnosing iron deficiency anemia (particularly if serum ferritin is inconclusive), folate or vitamin B12 deficiency anemia. Recently, a positive correlation had been proposed between RDW and both of morbidity and mortality in several disease states, principally in severely-ill patients. These conditions include renal disease, multiple cardiovascular diseases and interventions (such as coronary interventions), multiple sclerosis, and inflammatory bowel disease. This can be rationalized by the elevated levels of circulating inflammatory mediators **[6,7,8]**.

Recent studies have shown that RDW correlates significantly with the fibrosis stage in patients with NASH and chronic HBV infection **[9,10]**.

Multiple mechanisms are involved in the pathogenesis of HCV-related thrombocytopenia. The prevalence of thrombocytopenia in chronic HCV infection is estimated to be about 24%. In addition to eliciting an autoimmune reaction with production of anti-platelet antibodies, HCV has a direct bone marrow suppressing effect that eventually results in thrombocytopenia **[11]**.

PATIENTS AND METHODS

This retrospective study included 236 patients who had underwent liver biopsy for IFN-based therapy at National Liver Institute- Menoufia University during January 2014 to August 2014. After taking permission, we checked the files containing the clinical and lab data of these patients. Inclusion criteria: Patients aged 18-60 years old, no chronic medical disorders of cardiac, renal, collagen disease or malignancy with Hb% >12 g/dL, average TLC, Platelet count > 100.000 mm^3. Exclusion criteria: clinical data of any of the pre-defined medical disorders, Hb% <12 g/dL, abnormal TLC, Platelet count <100.000 mm^3, biopsy results of hepatic pathology other than HCV-related hepatocirrhosis. Based on these inclusion and exclusion criteria; 236 patients were selected and were classified into 4 groups according to the stage of cirrhosis reported by the liver biopsy examination according to Metavir score:

Group I (n=41): Patients with cirrhosis stages F0-F1

Group II (n=43): Patients with cirrhosis stage F2

Group III (n=48): Patients with cirrhosis stage F3

Group IV (n=104): Patients with cirrhosis stages F4

All laboratory results, (CBC, liver profiles and kidney functions) were tabulated for statistical analysis. In addition, the following ratios were calculated:

1) RPR was calculated from the following formula using RDW and platelet counts:

   RPR = RDW (%)/Platelet count (10^9/L) **[12].**

2) The FIB-4 index was calculated from the following formula:
   FIB-4 = (Age x AST) / (Platelet count x √ALT) **[13].**

3) The APRI was calculated from the following formula:

   ([AST [IU/L]/upper limit of normal] X 100/platelet count [10^9/L]) **[14].**

RESULTS

- 81% of the included patients were males (191/236), 19% of them were females (45/236), their ages ranged 22-58 years. There was a statistically-insignificant difference

between the studied groups regarding age and sex distribution (p>0.05) (Table 1).

- The mean ± SD for RDW, Platelet count, RPR, APRI and FIB-4 of the studied patients are tabulated in (Table 2). The results indicated that each mean value for RDW, Platelet count, RPR, APRI and FIB-4 were running progressively in correspondence with the stage of cirrhosis with a high statistically-significant difference (p<0.001).
- Statistical analysis of the results of HB%, platelet counts, transaminases, serum albumin, bilirubin, INR, and AFP levels revealed a high statistically-significant variation (p<0.001) that matches the progression of the stage of fibrosis. There was a statistically-insignificant difference regarding WBCs count and serum creatinine (p>0.05) (table 3).
- Using a cut-off value of 0.049; RPR can diagnose F2 stage of cirrhosis with a sensitivity of 84.23%, specificity of 61.74%, PPV of 69.2%, NPV of 78.1%. At a cut-off value of 0.074, RPR can diagnose F3 stage of cirrhosis with a sensitivity of 72.92%, specificity of 81.4%, PPV of 80.9%, NPV of 73.5%. At a cut-off value of 0.099, RPR can diagnose F4 stage of cirrhosis with a sensitivity of 88.46%, specificity of 75%, PPV of 85%, NPV of 75.4%.
- The results for diagnostic indices and cut-off values for RDW, platelet count, RPR, FIB4 and APRI are presented in (Table 4). RPR had sensitivity and specificity profiles that were more reasonable than APRI and FIB-4 at different stages of cirrhosis.
- AUROCs for the studied indices are shown in table 5. The AUROCs values for RPR were 0.795, 0.811 and 0.886 for F2, F3 and F4 stage of cirrhosis respectively. They were consistently higher than those of APRI (0.680, 0.754 and 0.746 for F2, F3 and F4 stages respectively) and FIB-4 (0.653, 0.765 and 0.810 for F2, F3 and F4 stages respectively). RPR was significantly-comparable to APRI (P<0.002), and FIB-4 (P<0.001) for the prediction of F3 stage of cirrhosis, and F4 stage of cirrhosis (P<0.001 & P=0.03 with APRI & FIB-4 respectively).

Table (1): Comparison between demographic data in the four groups.

		Group I (n=41)		Group II (n=43)		Group III (n=48)		Group IV (n=104)		ANOVA	P- Value
Age (years)	**X±SD**	40.98±12.370		40.23±7.622		43.02±8.017		41.46±7.270		0.869	0.458
	Range	22-55		32-58		25-52		31-53			
Sex		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**X^2**	P- Value
	Male	35	85.37	36	83.72	35	72.92	85	81.73		
	Female	6	14.63	7	16.27	13	27.08	19	18.27	2.412	0.491
	Total	41	100	43	100	48	100	104	100		

Table (2): Comparison between routine laboratory parameters in different fibrosis stages

	Group I (n=41)	Group II (n=43)	Group III (n=48)	Group IV (n=104)	F	P-value
Hb	15.934±0.852	14.786±1.648	14.892±1.446	13.900±1.618	19.595	< 0.001
RDW	13.989±0.793	14.262±1.446	14.967±1.024	15.854±1.524	2.661	0.045
TLC ($X10^3$)	6.839±1.876	6.746±1.952	7.504±1.887	5.971±2.211	6.643	0.563
Platelets ($X10^3$)	256.682±65.800	218.441±46.129	167.625±46.988	112.294±30.735	144.773	< 0.001
Creatinine	0.844±0.207	0.837±0.179	0.830±0.174	0.839±0.240	0.038	0.990
Albumin	4.417±0.161	4.328±0.291	4.188±0.270	3.821±0.494	34.487	<0.001
ALT	40.049±12.072	45.419±13.043	81.063±21.575	81.452±17.545	14.023	< 0.001
AST	32.951±11.715	37.930±11.432	93.875±23.783	105.539±29.315	24.847	< 0.001
Bilirubin	0.537±0.137	0.644±0.221	0.783±0.301	1.044±0.506	22.873	< 0.001
AFP	3.181±0.997	3.443±1.417	9.425±12.507	20.264±9.895	10.587	< 0.001
INR	1.081±0.040	1.037±0.079	1.071±0.107	1.146±0.155	10.415	< 0.001

Table (3): Values for each non-invasive method at each fibrosis stage.

	Group I (n=41)	Group II (n=43)	Group III (n=48)	Group III (n=104)	F	P-value
	X±SD	X±SD	X±SD	X±SD		
RPR	0.059±0.019	0.063±0.014	0.088±0.025	0.149±0.057	74.583	<0.001
APRI	0.276±0.082	0.400±0.188	1.320±0.705	2.272±1.430	57.194	<0.001
Fib4	0.854±0.260	1.062±0.378	2.822±1.109	4.713±1.968	108.558	<0.001

Table (4): Diagnostic performance of RPR, APRI and FIB-4 and their optimal cut-off values

	Stage	AUROC (95% CI)	Cut-off	Sensitivity %	Specificity %	PPV %	NPV %	+LR	-LR
RDW%	F2	0.680 (0.569-0.778)	13.5	72.09	80.49	96.9	25.3	3.69	0.35
	F3	0.733 (0.626-0.832)	13.9	66.67	67.44	69.5	64.5	2.05	0.49
	F4	0.761 (0.678-0.841)	14.5	55.77	0.83	80.5	42.5	1.61	0.62
Platelet X 10^9/L	F2	0.644 (0.532-0.745)	216	83.72	60.98	66.4	80.2	2.15	0.27
	F3	0.800 (0.703-0.876)	154	75.00	79.07	76.8	77.4	3.58	0.32
	F4	0.803 (0.731-0.863)	108	78.85	70.83	85.2	61.2	2.7	0.3
RPR	F2	0.795 (0.682-0.901)	0.049	84.23	61.74	69.2	78.1	2.15	0.27
	F3	0.811 (0.716-0.886)	0.074	72.92	81.4	80.9	73.5	1.96	0.5
	F4	0.855 (0.789-0.907)	0.099	88.46	75	85	75.4	3.92	0.33
APRI	F2	0.680 (0.569-0.777)	0.366	41.86	100	88.3	58.1	0.0	0.58
	F3	0.754 (0.688-0.787)	0.822	83.33	100	100	84.7	0.0	0.17
	F4	0.822 (0.699-0.813)	1.580	61.54	83.33	88.9	50	3.69	0.46
FIB-4	F2	0.653 (0.541-0.753)	1.24	78.21	100	100	59.2	0.0	0.63
	F3	0.765 (0.704-0.792)	1.6	87.50	93.02	93.3	87.0	12.54	0.13
	F4	0.762 (0.686-0.827)	2.92	85.58	62.5	82.9	67.1	2.28	0.23

Table (5): Correlations of AUROCs between RPR and other non-invasive predictors.

Fibrosis Stage	Models	AUROC (95% CI)	P value*
F2	RPR	0.795 (0.682-0.901)	
	RDW	0.680 (0.569-0.778)	0.297
	Platelet	0.644 (0.532 0.745)	0.636
	APRI	0.680 (0.569-0.777)	0.341
	Fib 4	0.653 (0.541-0.753)	0.494
F3	RPR	0.811 (0.716-0.886)	
	RDW	0.733 (0.626-0.832)	0.5817
	Platelet	0.800 (0.703-0.876)	0.028
	APRI	0.754 (0.688-0.787)	0.002
	Fib 4	0.765 (0.704-0.792)	< 0.001
F4	RPR	0.855 (0.789-0.907)	
	RDW	0.761 (0.678-0.841)	< 0.032
	Platelet	0.803 (0.731-0.863)	< 0.001
	APRI	0.822 (0.699-0.813)	< 0.001
	Fib 4	0.762 (0.686-0.827)	0.03

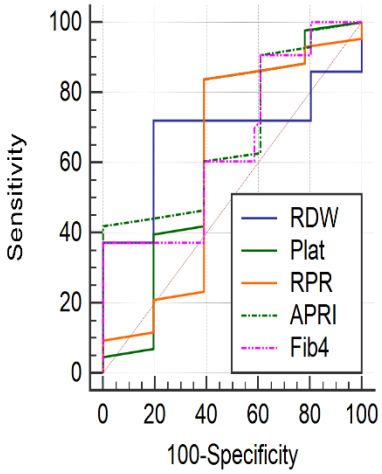

Figure 1: ROC curve for different predictors for F2 stage of cirrhosis.

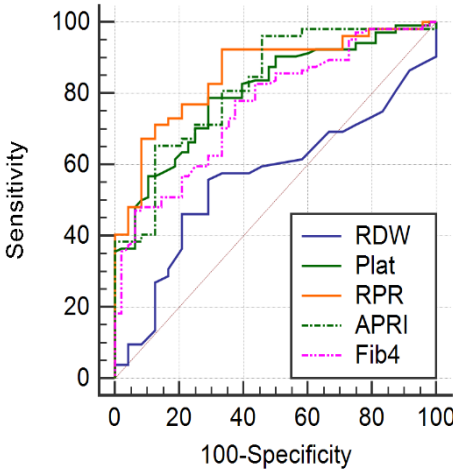

Figure 2: ROC curve for different predictors for F3 stage of cirrhosis.

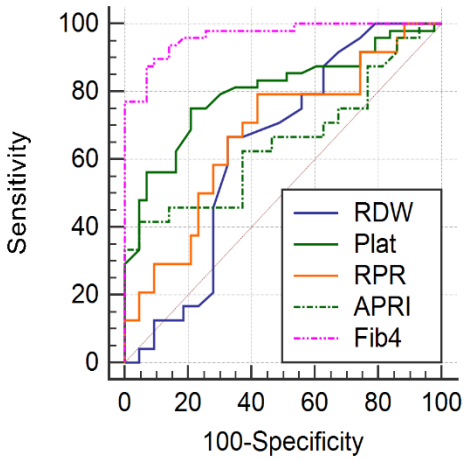

Figure 3: ROC curve for different predictors for F4 stage of cirrhosis.

DISCUSSION

HCV infection is almost always progressive either to hepatitis, cirrhosis. Liver biopsy is the definite method for staging hepatic cirrhosis. However, it is invasive and has several limiting contraindications (e.g. bleeding tendency, ascites, hemodynamically-unstable patients) **[15].**

The clinical implications of different components of CBC have been extensively studied and proved reasonable significance in prediction of disease severity or mortality risk. RDW has been reported to be concomitantly-elevated with increased mortality or poor outcomes of several diseases **[16,17]**, and platelet count is an undebatable, dependable and simple predictor of hepatic fibrosis. It has been included in most of the predictive models for estimating hepatic fibrosis and cirrhosis **[11].** Thus, the impregnation of these 2 parameters in a single equation is expected to yield a new index with higher diagnostic indices than any of the 2 parameters solely. Moreover, unlike APRI or FIB-4 scores, RPR is not influenced by the variation in transaminases levels which may fluctuate with disease activity or when other offending factors exist e.g. drug-induced liver injury.

In 2013, **Chen** et al. released a novel, simple and low-cost index that yielded a promising role in predicting the stage of cirrhosis in patients with CHB. This index includes only two variables that are routinely reported in the CBC, which are RDW and platelet count **[12].**

Before starting our study, we searched the published data about RPR and we found many studies about its role in staging hepatic cirrhosis in patients with HBV-related liver diseases, NAFLD and PBC. Because of the too many numbers of HCV cases in Egypt, we decided to conduct a similar study on HCV-infected patients to validate RPR usefulness in this category of liver-diseased patients. It was proposed that if proved promising; RPR will be extensively helpful in clinical practice for predicting the degree of hepatic cirrhosis in patients with HCV-related cirrhosis specially when TE is not available.

There was a high statistically-significant difference between the studied groups regarding RDW%, platelet count and RPR (table 3). This indicates that these indices run parallel with the progression of liver injury. In agreement with these results, **Huang et al.** reported that RDW could be a dependable indicator for predicting disease severity and they defined a cut-off of 16.07±2.41%, 13.29±1.09% and 12.75±0.70% for patients with HBV- related liver cirrhosis, non-cirrhotic CHB patients and healthy controls respectively **[18].**

Moreover; **Lou et al.** reported that RDW increases significantly in patients with chronic

active HBV infection than in healthy controls. In addition, they reported that RDW in this population could predict a 3-month mortality risk **[17].**

In agreement with our results, **Jin et al.** reported that RDW and RPR rates are significantly-higher in patients with HCV-related cirrhosis than in those with non-active chronic HCV infection and healthy controls. In addition, they concluded that the RDW rates were significantly-correlated with the severity of liver disease estimated by MELD and CTP scores **[19].**

Though having higher AUROCs than FIB-4 and APRI score, RPR was insignificantly-comparable to FIB-4 (P=0.494) and APRI (P=0.341), for the prediction of early cirrhosis (< F2 stage of cirrhosis) but RPR was significantly-correlated to APRI (P<0.002), and FIB-4 (P<0.001) for the prediction of F3 stage of cirrhosis, and F4 stage of cirrhosis (P<0.001 & P=0.03 with APRI & FIB-4 respectively). This can be rationalized by the inclusion of transaminases in both scores and its absence in RPR. Being released from other tissues (e.g. RBCs, myocardium), AST may give over- or less-predicting results about hepatic injury.

In agreement with these results, **Lee et al.** reported a good diagnostic performance of RPR (AUROC=0.801) in predicting significant fibrosis (≥F2) and cirrhosis (F4) in patients with CHB that was comparable to FIB-4 (AUROC=0.811) and superior to APRI (AUROC=0.680) for diagnosing F4 stage of cirrhosis **[20].**

Also, **Wang et al.** concluded that RPR yielded a higher AUROC (0.711) than APRI (0.648; *P* = 0.035) and FIB-4 (0.682; *P* = 0.009) in prediction of F4 stage of cirrhosis in patients with primary biliary cirrhosis **[21].**

Karagöz et al. reported an AUROC of 0.705 for RPR for predicting significant fibrosis (>F3) in chronic HCV-infected patients, which was superior to the APRI score of the studied groups **[22].**

There was a statistically-insignificant difference regarding TLC of the studied groups in this study. In contrast, **Alkhouri et al.** concluded that TLC was significantly-correlated with disease severity in patients with NASH. This could be due to different etiology of liver disease between both studies **[23].**

CONCLUSION

RPR is a cost-effective, dependable, non-invasive tool for the estimation of liver fibrosis in HCV-infected patients. RPR proved to be comparable to FIB-4 and superior to APRI score in our study. RPR may be used as an alternative for liver biopsy in patients with HCV, especially when TE is not available.

List of Abbreviations:
Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), Direct Acting Antivirals (DAAs), Interferon (IFN), Hepatocellular carcinoma (HCC), Fibrosis score based on 4 factors (FIB-4), Red blood cells (RBCs), RBC distribution width (RDW), RBCs distribution width/ Platelet Ratio (RPR), Aspartate aminotransferase (AST)-to-platelet ratio score (APRI), Transient Elastography (TE), World Health Organization (WHO), Chronic Hepatitis B (CHB), Non-Alcoholic Steatohepatitis (NASH), Hemoglobin (Hb), Total leucocytic Count (TLC), Complete Blood Count (CBC), Model for End-Stage Liver Disease score (MELD score), Child-Turcott-Pugh score (CTP score).

Highlights

- Liver biopsy is the gold standard for assessing hepatic histology including staging hepatic cirrhosis. However, its invasive nature, risk of minor and major complications, intra- and inter-observer variability and sampling error makes it inconvenient to all cases.
- The need for non-invasive models have resulted in development of several models that compete each other in the simplicity, availability and cost issues.
- Of the most emerging models, RPR has the benefit of not depending on transaminases, low cost, and having promising diagnostic profiles when compared to traditional models like APRI score and FIB-4.

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Conflict of Interest: the authors declare that there was no conflict of interest.

Ethical consideration:

This study was carried out in conformity with the Declaration of Helsinki. The study protocol was notarized by the Ethics Committee of the Faculty of Medicine, and National Liver Institute, Menoufia University.

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