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Original article

The Ratio between Red Cell Distribution Width to Platelets as Predictor for Hepatic Fibrosis in Non- alcoholic Fatty Liver Disease in Egyptian Patients

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Abstract

Background: patients with non-alcoholic fatty liver disease (NAFLD) are commonly asymptomatic and identified incidentally. Liver biopsy is the gold standard for diagnosing non-alcoholic fatty liver. However this method is not only invasive and expensive but also has important limitations, including pain, patient's reluctance and risk of severe complications. Additionally, the platelet count and platelet-related indices, such as the Age-platelet (AP) Index, AST to Platelet Ratio(APRI) Index, and Fibrosis-4 (FIB4) Index have been widely used to evaluate the severity of various liver diseases but less accurate. **Aim** of the work: To assess the red cell distribution width-to-platelet ratio as a predictor of liver fibrosis in patients with NAFLD. **Material and methods**: This prospective study was conducted on a selected group of 125 patients. All patients underwent a thorough history taking, comprehensive clinical examination, body mass index assessment and laboratory investigation including complete blood count (CBC), RDW to platelet ratio (RPR) calculated as RDW multiplied by 100 divided by platelet (109/L), ALT, AST, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c). Additionally, imaging studies such as Pelvi-abdominal U/S and Fibroscan were performed. Results: Severe fibrosis was associated with diabetes, increased BMI, decreased platelet count, elevated RDW/PLT ratio and elevated ALT and AST. There was a positive correlation between RPR and increased age, obesity, increased RDW and AST and advanced fibrosis. However, there was a negative correlation with male gender, decreased platelet count and decreased TLC. Conclusion: RPR is a good predictor for liver fibrosis in NAFLD patients

Keywords: Non-alcoholic fatty liver; NAFLD; RPR; Fibroscan

Abbreviations: ALT : Alanine transaminase. , AST: Aspartate transaminase. ,RDW: Red Cell Distribution Width. TLC Total Leucocytic Count

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a global health issue that affects over 25% of the world's population. Reports indicate that, the Middle East has the highest prevalence of NAFLD at 31.79%[1]. On the other hand Africa has the lowest prevalence rate at 13.48% [2]. In Egypt, NAFLD is more common in men (31%) than in women (16%) and its prevalence increases with age. It is less than 20% among individuals under 20 and exceeds 40% among those over 60 years old [3]. Aspartate-aminotransferase (AST) or alanine aminotransferase (ALT) elevations, which are typically noted during routine laboratory examinations or abnormal imaging studies done for other reasons, are the most common reasons that patients with NAFLD are brought to the attention the clinician[4]. Patients may also complain of fatigue and dull aching pain in the right upper abdomen [5]. Red blood cell distribution width (RDW) is an automated measure of red cell size heterogeneity (e.g. anisocytosis) and is routinely performed as part of a complete blood count. RDW is used in the differential diagnosis of anemia [6]. Several studies have shown that RDW can serve as a new independent predictor of prognosis in patients with cardiovascular disease such as heart failure, stable coronary artery disease, acute myocardial infarction, stroke and pulmonary hypertension[7].

High RDW values have also been shown to be associated with an increased risk of mortality in the general population. However, the relationship between RDW and NAFLD is uncertain. If future follow-up studies confirm this association, it could justify incorporating RDW into NAFLD risk prediction algorithms [8]. The production of peripheral platelets is mainly regulated by thrombopoietin, a glycoprotein hormone synthesized in the liver. Previous studies have reported an inverse correlation between the degree of chronic hepatitis and the number of peripheral platelets [9]. Platelet count itself and platelet indices like AP index, APRI index and FIB4 index have been widely used to assess the severity of various liver diseases, particularly in patients with chronic hepatitis B or C virus infection [10]. However, the effect of NAFLD on platelet count is controversial. The results of numerous studies suggest that platelet count could serve as an ideal biomarker for fibrosis severity in patients with NAFLD [11].

Several studies have shown the RDW to platelet ratio (RPR) in liver disorders and analyzed its efficiency in predicting severity of liver fibrosis and cirrhosis [12].

The aim of this study was to investigate the red cell distribution width-to-platelet ratio as a potential marker for liver fibrosis in patients with non-alcoholic fatty liver disease.

Patients and Methods

This was a cross-sectional study which that included 125 participants who attended National Hepatology and Tropical Medicine Research Institute in Cairo, Egypt from September 2022 to December 2022. Approval from the GOTHI Medical Ethical Committee (approval number: ITH 00140) and the Benha Medical Ethical Committee (MS 45-9-2022) was obtained, and each

participant signed a written informed consent.

Patients aged 18 years and older, diagnosed with non-alcoholic fatty liver disease, were included in this study. However patients who consume alcohol, have viral hepatitis, metabolic liver diseases, renal insufficiency, cancer, are pregnant or have been recently infected were excluded.

All participants underwent a full history taking, comprehensive clinical examination, body mass index assessment, and laboratory investigations including complete blood count (CBC), RDW to platelet ratio (RPR) calculated as RDW multiplied by 100 divided by platelet (10^9/L), ALT, AST, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c). Additionally, imaging studies such as Pelvi-abdominal U/S and Transient elastography were conducted.

Pelvi-Abdominal ultrasound examinations was performed by experienced radiologists who was unaware of the clinical and laboratory data, using Hitachi A Vius Sonography machine with a convex probe (Hitachi, USA) Specifically, hepatic steatosis was diagnosed according to characteristic echo patterns, such as diffuse hyperechogenicity of the liver relative to the kidneys, ultrasound beam attenuation, and poor visualization of intrahepatic structures. Hepatic steatosis was diagnosed according to the guidelines established for the diagnosis and treatment of NAFLD **(13)**

Grading of non-alcoholic fatty liver on ultrasonography:-

- **Grade I:** Minimal diffuse increase in the fine echoes. Liver appears bright compared to the cortex of the kidney. Normal visualization of diaphragm and intrahepatic vessel borders.
- **Grade II:** Moderate diffuse increase in the fine echoes. Slightly impaired visualization of the intrahepatic vessels and diaphragm
- **Grade III:** Marked increase in the fine echoes. Poor or no visualization of intrahepatic vessels and diaphragm and poor penetration of the posterior, segment of the right lobe of the liver (14)

Transient elastography (TE) using **Echosens fibroscan 502** (Echosens, France).

This method allows for the evaluation of numerous parameters including velocity of vibration, velocity of wave propagation, and elastic modulus. TE allows for the identification of disease severity due to altered mechanical properties of the fibrotic liver **(15)**

- Fibrosis score F0 to F1: No liver scarring or mild liver scarring
- Fibrosis score F2: Moderate liver scarring
- Fibrosis score F3: Severe liver scarring
- Fibrosis score F4: Advanced liver scarring (cirrhosis)

Statistical analysis

The statistical analysis was conducted by using statistical SPSS Package program version 24 for Windows (SPSS, Inc., Chicago, IL). The following statistical procedures were conducted:

Chi-square test (χ2- test), unpaired (independent) t-test, Spearman correlation

coefficient analysis, Univariate and multivariate logistic regression analysis and Receiver operator curve (ROC).

Significant level: all statistical analyses were significant at 0.05 level of probability ($P \leq 0.05$).

Results

In the current study, patients were divided into two groups according to fibroscan results: Group 1, the Mild – Moderate group (F0-F1-F2), and Group 2, the severe group (F3-F4). The mean age of both groups was 45 years old. It was observed that severe fibrosis was more common in females.

Severe fibrosis was associated with diabetes and obesity showing a statistically significant difference compared to the other group (**Table 1).**

Additionally, a decrease in platelet count, an elevated RDW/PLT ratio and elevated ALT and AST were associated with severe fibrosis, also showing a statistically significant difference compared to the other group **(Table 2).**

There is a positive correlation between RPR and increasing age, obesity, Hb levels, RDW levels and AST levels and advanced fibrosis. On the other hand there is a negative correlation with male gender, decreasing platelet count and decreasing TLC **(Table 3)**.

Age≥45 years old, RDW/Platelets Ratio ≥0.048 and AST ≥ 31.5 are independent predictor factors of liver fibrosis (**Table 4).** The best cut-off value for the red cell distribution width-to-platelet ratio (RPR) that achieves the highest sensitivity (91.50%) and specificity (70.50%) is 0.048 with an accuracy of 91.79% to predict liver fibrosis in patients with NAFLD **(Table 5) & (Figure 1).**

Table (1): Demographic criteria and clinical picture of patients.

Patients history		Group 1 Mild – Moderate group (F0-F1-F2) n=(78)	Group 2 Sever group (F3-F4) n =(47)	Statistic test-value	P-value
Age (year)		**45.65 ±6.84**	**45.09 ±5.12**	**0.512**	**0.610**
Gender	**Males**	**26 (33.30%)**	**15 (31.90%)**	**0.027**	**0.870**
	Females	**52 (66.70%)**	**32 (68.10%)**		
Diabetic	**Yes**	**13 (16.70%)**	**25 (53.20%)**	**18.492**	**0.0001***
	No	**65 (83.30%)**	**22 (46.80%)**		
HTN	**Yes**	**5 (6.40%)**	**7 (14.90%%)**	**2.432**	**0.119**
	No	**73 (96.60%)**	**40 (85.10%)**		
Smoking	**Yes**	**5 (6.40%)**	**2 (4.30%)**	**0.258**	**0.612**
	No	**73 (93.60%)**	**45 (95.70%)**		
Weight (kg)		89.16 ±2.49	90.62 ±2.68	3.138	0.002*
Height (cm)		168.68 ±2.37	168.77 ±1.60	0.257	0.797
BMI (kg/m^2)		30.64 ±0.64	31.09 ±0.96	2.846	0.006*
Systolic blood pressure (mm/Hg)		129.59 ±3.95	131.00 ±4.93	1.664	0.100
Diastolic blood pressure (mm/Hg)		84.67 ±3.03	85.59 ±5.25	1.097	0.277
Hepatomegaly	**Yes**	53 (67.90%)	30 (63.80)	0.223	0.637
	No	25 (32.10%)	17 (36.20%)		

HTN: Hypertension BMI: Body Mass Index

Table (2): Laboratory investigations of the studied patients.

Examinations	Group 1	Group 2	t-value	P-value
Hb (g/dl)	13.13 ±0.58	13.29 ±0.94	1.047	0.299
TLC (c/mm^3)	6.93 ±1.41	6.74 ±0.92	0.911	0.364
Platelet (c/mm^3)	272.41 ±41.10	239.41 ±40.91	4.360	0.0001*
RDW%	13.49 ±1.15	13.37 ±0.81	0.639	0.524
RDW / PLT ratio	0.049 ±0.008	0.059 ±0.013	3.347	0.001*
ALT (IU/dl**)**	34.30 ±13.47	41.05 ±14.73	2.562	0.012*
AST (IU/dl**)**	31.89 ±9.18	36.42 ±16.24	1.992	0.049*
Total cholesterol (mg/dl)	179.73 ±21.61	187.32 ±29.26	1.545	0.127
Triglycerides (mg/dl)	142.59 ±36.50	153.27 ±61.25	1.085	0.282
LDL (mg/dl)	107.86 ±19.78	115.38 ±26.70	1.674	0.098
HDL (mg/dl)	45.06 ±5.43	47.39 ±5.31	2.350	0.21

HB**:** Hemoglobin TLC: Total Leucocytic Count RDW: Red Cell Distribution Width LDL: Low Density Lipoprotein HDL: High Density Lipoprotein

Table 3: Correlation between red cell distribution width-to-platelet ratio (RPR) and various parameters.

Items	Correlation coefficient (r)	P-value
Age (year)	0.494	0.001*
Male gender	-0.283	0.004*
Weight (kg)	0.248	0.005*
Height (cm)	0.116	0.197
BMI (kg/m^2)	0.139	0.123
Systolic blood pressure (mm/Hg)	0.018	0.845
Diastolic blood pressure (mm/Hg)	0.025	0.779
Hb (g/dl)	0.157	0.002*
TLC (c/mm^3)	-0.354	0.0001*
Platelet (c/mm^3)	-0.842	0.0001*
RDW %	0.239	0.007*
ALT (IU/dl)	0.129	0.150
AST (IU/dl)	0.182	0.042*
Total cholesterol (mg/dl)	0.067	0.458
Triglycerides (mg/dl)	-0.070	0.435
LDL (mg/dl)	0.016	0.860
HDL (mg/dl)	0.102	0.258
Severe fibrosis	0.493	0.0001*

Table 4: Regression analysis of dependent variables for predicting advanced fibrosis by red cell distribution width-to-platelet ratio (RPR).

Items	Univariate logistic regression model		Multiple logistic regression model	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Age (year)	0.63 (0.60 – 1.05)	0.006*	0.97 (0.45 – 1.08)	0.014*
Male gender	1.01 (0.46 – 2.19)	0.987	1.02 (0.45 – 2.13)	0.951
Weight (kg)	1.32 (1.09 – 1.60)	0.004*	1.25 (0.97 – 1.62)	0.087
Height (cm)	1.02 (0.86 – 1.21)	0.813	1.04 (0.77 – 1.38)	0.818
BMI (kg/m^2)	2.88 (1.27 – 6.56)	0.011*	2.00 (0.75 – 5.31)	0.167
Systolic blood pressure (mm/Hg)	1.08 (0.98 – 1.19)	0.096	1.12 (0.92 – 1.37)	0.274
Diastolic blood pressure (mm/Hg)	1.06 (0.96 – 1.17)	0.222	0.92 (0.76 – 1.10)	0.351
Hb (g/dl)	1.34 (0.82 – 2.21)	0.245	1.54 (0.80 – 2.96)	0.192
TLC (c/mm^3)	0.88 (0.65 – 1.19)	0.410	1.39 (0.89 – 2.16)	0.143
Platelet (c/mm^3)	0.98 (0.96 – 0.99)	0.0001*	0.96 (0.93 – 1.00)	0.064
RDW %	0.90 (0.93 – 1.00)	0.0001*	1.36 (0.65 – 2.87)	0.416
RDW / platelet ratio	0.14 (0.11 – 0.19)	0.002*	0.17 (0.15 – 0.49)	0.001*
ALT (IU/dl)	1.13 (0.99 – 1.27)	0.074	1.20 (1.02 – 1.32)	0.997
AST (IU/dl)	1.04 (1.01 – 1.07)	0.017*	0.16 (1.00 – 1.53)	0.011*
Total cholesterol (mg/dl)	1.01 (0.99 – 1.03)	0.113	0.99 (0.95 – 1.03)	0.564
Triglycerides (mg/dl)	0.91 (0.97 – 1.00)	0.236	1.01 (0.99 – 1.02)	0.237
LDL (mg/dl)	1.02 (1.00 -1.03)	0.088	1.02 (0.98 – 1.06)	0.295
HDL (mg/dl)	1.09 (1.01 – 1.18)	0. 27	1.08 (1.00 – 1.17)	0.054

Table 5 &Figure 1: Receiver operator curve (ROC) of red cell distribution width-to-platelet ratio (RPR) for prediction of liver fibrosis.

Variables	RDW / Platelet ratio (RPR)
Best cut off	0.048
Area under curve (AUC)	0.787
95% CI	0.701 – 0.873
Sensitivity	91.50%
Specificity	70.50%
Accuracy	91.79%
P-value	0.0001*
Significance (P<0.05)	S

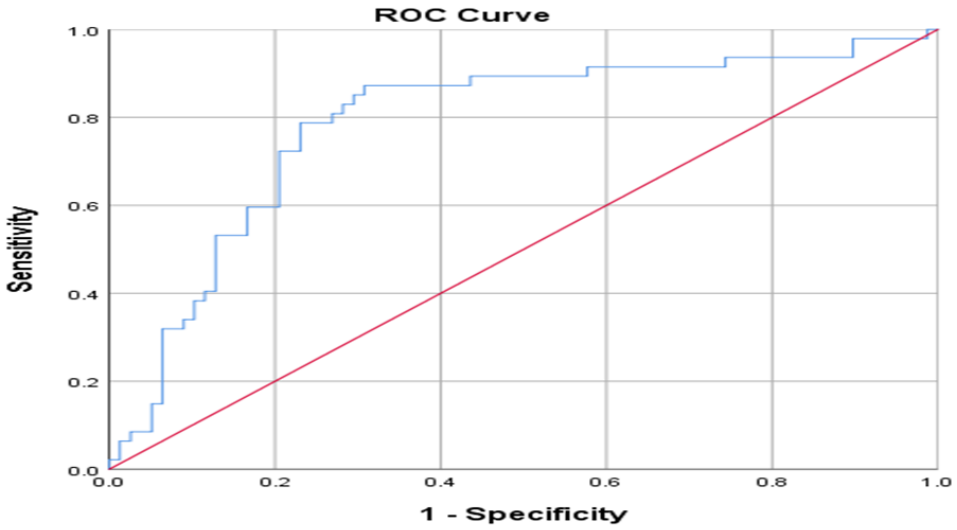

Figure (1): ROC Curve of RPR to predict liver fibrosis in patients with NAFLD.

Discussion

NAFLD is defined as the abnormal accumulation of fat (>5%) in the hepatocytes without significant alcohol consumption (>30 g/d in men, >20 g/d in women[16].

The term metabolic dysfunction-associated steatotic liver disease (MASLD) has superseded the term nonalcoholic fatty liver disease. Patients with hepatic steatosis who also have at least one of the five cardiometabolic risk markers are classified as having MASLD.

Beyond pure MASLD, a new group called MetALD was chosen to characterize MASLD patients who drink more alcohol on a weekly basis (140 g for women and 210 g for men, respectively).

NASH has been replaced with metabolic dysfunction-associated steatohepatitis (MASH). Cryptogenic Steatotic liver

disease (SLD) is characterized by the absence of metabolic markers and an unknown cause[17].

A nationwide study in Sweden revealed that all histological stages of NAFLD are associated with a significantly increased overall mortality with the risk increasing as the degree of fibrosis worsens. The excess mortality linked to NAFLD was primarily caused by extrahepatic cancer followed by cirrhosis, cardiovascular disease, and HCC[18].

Several studies have reported an inverse correlation between the degree of chronic hepatitis and the number of peripheral platelets[19].

Several investigators have studied the RDW to platelet ratio (RPR) in liver disorders and analyzed its effectiveness in predicting the severity of liver fibrosis and cirrhosis[20].

This study showed that female gender was associated with advanced fibrosis **(Table 1) which is consistent** with the finding of others [21]. It was reported that in cases of NAFLD, women have a 37% higher risk of advanced fibrosis compared to men.

This current study demonstrated a statistically significant difference in DM between severe and mild to moderate liver fibrosis **(Table 1)**. This finding came in agreement with the systematic review and meta-analysis done in 2019 [22] where it was reported that the prevalence of NAFLD in T2DM patients was approximately 55.5%, with a high proportion of severe liver fibrosis at 17.7%.

Furthermore, our study found a statistically significant difference in BMI between severe fibrosis and mild to moderate fibrosis **(Table 1).** This finding was in line with other researchers [23] who discovered an association between increased BMI and fibrosis progression. Additionally, another study by [24] found that high BMI predicted liver fibrosis in obese children and adolescents.

Our study found a statistically significant difference in platelets count between severe fibrosis and mild to moderate fibrosis **(Table 2)**. This was consistent with the finding scientists who also found that platelet count can predict severe stages of liver fibrosis [25 and 26].

The current study showed that the ratio between red cell distribution width and platelets (RPR) is statistically significant in comparing severe and mild to moderate NAFLD fibrosis **(Table 2).** This finding aligned with the results of the observational study published in 2015 **on** RPR in NAFLD. As the fibrosis scores increased, the median values of RPR also increased [20].

The present study demonstrated that increased ALT levels are statistically significant when comparing severe fibrosis and mild to moderate fibrosis in NAFLD patients **(Table 2).** This result agreed with the research conducted in 2021which emphasizes that the contribution of ALT as an independent factor for detecting NAFLD fibrosis, is small [27].

Another study discovered that ALT and AST activities were significantly higher in T2D patients with NAFLD compared to T2D patients without NAFLD. Additionally, elevated serum AST levels were associated with an increased risk of liver fibrosis [28].

In this present study we found that hyperlipidemia was not associated with

fibrosis, and there was no statistically significant difference in cholesterol, triglycerides and LDL levels between the two groups **(Table 2)**. This finding was in agreement with the study which showed a significant positive correlation between the presence of NAFLD and increasing levels of serum total cholesterol LDL and triglyceride and a significant decrease in HDL. However, they did not find a significant positive correlation between the grading of fatty liver and the level of different components of the lipid profile[29]. On the other hand it was reported that as the grade of NAFLD increased, there was a significant increase in levels of serum total cholesterol, TG, LDL and VLDL. It is worth noting that this difference may be attributed to the fact that the patients in our study were on antihyperlipidemic medication at the time of the study[30].

Our study revealed a significant positive correlation between RPR and several parameters, including increasing age, obesity, increased RDW and advanced fibrosis. Additionally, we found a significant negative correlation with male gender, decreased platelet count and decreased TLC count **(Table 4).**

This finding lined with a study done on 2019**,** which also reported a significant positive correlation between RPR and increasing age, creatinine and Hb, as well as a significant negative correlation with WBC count, sex [31].

Furthermore, our study determined that at a cut-off of 0.048, RPR had a sensitivity and specificity of 91.5% and 70.5%, respectively, with accuracy 91.79 % to predict liver fibrosis **(Table 5) & Figure1.** This result came in line with the findings of [32] who concluded that RPR has good accuracy in detecting significant fibrosis, advanced fibrosis and cirrhosis in patients with chronic liver disease.

Conclusion

Severe fibrosis was associated with diabetes, obesity decreased platelet count, elevated RDW/PLT ratio, and elevated ALT, AST in NAFLD patients. Age≥45 years old, AST ≥ 31.5 and RDW/Platelets Ratio ≥0.048 are independent predictor factors of liver fibrosis. RPR is a good predictor for liver fibrosis in NAFLD patients.

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