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ORIGINAL ARTICLE

Clinical Significance of Red Distribution Width to Platelet Ratio in Evaluation of Hepatic Fibrosis in Metabolic Dysfunction Associated Fatty Liver Disease

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Abstract

Background: ***In 2020, the abbreviation "metabolic dysfunction-associated fatty liver diseases" (MAFLD) was employed to denote hepatic steatosis associated with systemic metabolic dysfunction.***

Aim and objectives: ***To evaluate the diagnostic and clinical use of the width of red cell distribution to platelet ratio as a noninvasive surrogate marker for liver stiffness in fatty liver diseases linked to metabolic dysfunction.***

Patients and methods: ***The current cross-sectional study was carried out on 100 MAFLD patients presented in the MAFLD outpatients' clinic, National Hepatology and Tropical Medicine Research Institute (NHTMRI) incorporation with El-Hussein University hospital-internal medicine department from March to August 2023.***

Results: ***The highest mean value of Red cell distribution width to platelet ratio (RPR) was higher in Fibrosis F4 (0.107±0.016), followed by Fibrosis F3 (0.098±0.013), then Fibrosis F2 (0.070±0.025), with the most negligible value recorded in F1 (0.044±0.012). RPR can be a noninvasive diagnosis indicator for predicting extensive fibrosis in patients with NAFLD.***

Conclusion: ***RPR is a straightforward and readily accessible measure for estimating the severity of MAFLD disease. When predicting MAFLD, the RPR index outperforms FAST, FIB-4, and APRI due to its greater AUC. In patients with MAFLD, RPR can be employed as a noninvasive diagnosis marker to forecast severe fibrosis.***

Keywords: Red Distribution Width; Platelet ratio; hepatic fibrosis; metabolic dysfunction

1. Introduction

In 2020, the abbreviation "metabolic dysfunction-associated fatty liver diseases" (MAFLD) referred to fatty liver disease linked to systemic metabolic dysregulation. The change in the name of nonalcoholic fatty liver disease (NAFLD) to MAFLD has incorporated a clear and precise set of criteria, making it easier for general practitioners, including primary care physicians, to diagnose patients at the bedside.[1]

Numerous studies have revealed that co-morbidities related to metabolism, including obesity, type 2 diabetes, heart disease, dyslipidemia, hypertension, metabolic syndrome, hypothyroidism, polycystic ovarian syndrome, and obstructive sleep apnea syndrome, are significant risk factors for multiple sclerosis.[2]

It includes a broad range of histological patterns, including fibrosis, cirrhosis, steatohepatitis, and simple steatosis.[3]

Younossi et al. reported that the global prevalence of MAFLD is currently estimated to be 25%. South America has the highest prevalence of MAFLD at 30.5%, followed by the Middle East at 31.8%. Asia has a prevalence of 27.3%, while the USA and Europe have rates of 24% and 23.7% respectively. Africa has the lowest incidence at 13.5%.[4]

The METAVIR scoring system is the most widely used histological approach for evaluating liver fibrosis. It categorizes fibrosis into five stages: no fibrosis (F0), mild fibrosis (F1), significant fibrosis (F2), severe fibrosis (F3), and cirrhosis (F4). Liver biopsy is the prevailing technique for identifying liver fibrosis. Recent research has revealed that a significant proportion, ranging from 10% to 30%, of cases with liver fibrosis may be incorrectly diagnosed in a single liver biopsy, hence disregarding potential consequences.[5]

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In standard dynamic clinical practice, noninvasive blood biomarkers are more chosen by patients and clinicians due to their simplicity, accessibility, and repeatability. The diversity in erythrocyte size in peripheral blood is measured by red cell distribution width (RDW) (Anisocytosis).[6]

According to several studies, the platelet count can independently predict the presence of liver cirrhosis and the extent of fibrosis in individuals diagnosed with MAFLD and NASH; additionally, various MAFLD fibrosis grading systems for adults, including FIB4, APRI, and fibro index score, now include platelet count.[7]

2. Patients and methods

Between March and August 2023, 100 MAFLD patients who had been seen at the MAFLD outpatients' clinic at El-Hussein University Hospital's internal medicine department and The NHTMRI refers to the National Hepatic and Tropical Medicine Researchers Institute were included in the current cross-sectional study. Before the patients were enrolled in the trial, they completed an informed consent form (ICF). Following this, laboratory and imaging work-ups were performed. The individuals were evaluated for three out of five criteria indicating dysregulation of metabolism in the context of fatty liver disease, which is linked to metabolic dysfunction (MAFLD).

≥90/80 cm for Asian men and women, or ≥102/88 cm for Caucasian men and women)*. BP ≥130/85 mmHg or a particular medication regimen. Triglycerides in plasma ≥ 150 mg/dL or a certain medication regimen. Forty mg/dL for men and fifty mg/dL for women in plasma HDL cholesterol or a specified medication regimen. Prediabetes is defined as HbA1c 5.7% to 6.4%, fasting glucose levels of 100 to 125 mg/dL, or 2-hour post-load glucose levels of 140 to 199 mg/dL. Assessment of the homeostasis model (HOMA)A score of ≥2.5 for insulin resistance. >2 mg/L of plasma high-sensitivity C-reactive protein (hs-CRP).[8]

Inclusion Criteria: Patients who are over the Age of 18, have increased liver enzymes, and have fatty liver seen on imaging tests such as fibro-CAP and abdominopelvic ultrasonography.

Exclusion Criteria: Wilson's disease, Celiac disease, HCV infection, anaemia, hematologic malignancies, and continuous drinking (male: >30g/day, female: >20g/day) are all excluded. Drugs: methotrexate, amiodarone, tamoxifen, valproic acid, IUD, and hemochromatosis. Prolonged utilization of immunosuppressive drugs or substances that can modify liver functionality, hypo- or hyperthyroidism, gastric bypass surgery, and complete parenteral feeding.

Ethical Considerations:

The Institutional Review Board (IRB) of the National Hepatic and Tropical Medicine Research Institute (NHTMRI) and the Ethics Committee of the Board of the Faculty of Medicine at Al-Azhar University, and the GCP guidelines and the Declaration of Helsinki were all followed in the conduct of the study. The participant gave his written informed consent after being led to a quiet, private area where he was briefed on the study's goals and methods in plain language and had his queries addressed.

METHODS: Every sufferer endured the following:

Complete medical history including Age, gender, employment, history of diabetes and hypertension, right hypochondrial pain, existence of any concomitant diseases, surgical background, history of smoking, drinking, or abusing drugs, and dietary habits.

Clinical examination:

General examination of height, weight, BMI and waist circumference.

Anthropometric measurement: BMI will be calculated as weight (kilograms) divided by the square of height (meters). Severely underweight-underweight-normal-overweight-obesity class I-classII-class III BMI < 16.5 - < 18.5 - ≥18.5 to 24.9 - ≥25 to 29.9 - ≥30 - 30 to 34.9 -35 to 39.9 - ≥40 kg/m2 respectively.[9]

Local examination with stress on right hypochondriac pain.

Laboratory investigations: Complete blood count (CBC): Normal values of haemoglobin level Liver profile (AST, ALT, Total bilirubin)). Serum creatinine, HBs Ag, HCV Ab, anti-nuclear antibody, total Immunoglobulin G, fasting blood sugar, lipid profile: total cholesterol, triglycerides, HDL, LDL and finally, FIB 4 (Fibrosis 4), APRI (AST platelet ratio index) and FAST scores (Fibrosis AST) measurements.

FIB4:

$$\text{FIB-4 Score} = (\text{Age} \times \text{AST}) / (\text{Platelets} \times \sqrt{(\text{ALT})})$$

(Sterling et al 2006).[10]

AST platelet ratio index (APRI):

$$\text{APRI} = [\text{AST/AST (ULN)}] / \text{platelet (109/L)}$$

(Castillo et al 2008).[11]

FAST scores:

(Newsome et al. 2020).[12]

Radiological investigations:

Pelvi-abdominal sonography: The evaluation for fatty liver will be based on five criteria: deep beam attenuation, liver-to-kidney contrast, parenchymal brightness, brilliant vessel walls, and gallbladder wall characterization. These five factors will be

employed in an algorithm to produce an overall evaluation of ordinary vs steatosis.[13]

Hepatic ultrasound elastography (fibro scan) to determine the extent of hepatic fibrosis. Position the transducer across the intercostal space when the patient is lying on their back or left side, with the right arm raised above the head to enlarge the intercostal acoustic window. The measurement will be made during a brief breath hold (a few seconds) to optimize the results. This is because deep breathing and the Valsalva manoeuvre both alter the hepatic venous pressure, which can change the assessment of stiffness. Measure of liver steatosis Decibels per meter (dB/m) is the unit of measurement for the controlled attenuation parameter (CAP), which varies from 100 to 400 dB/m.[14]

For S0 no steatosis, S1 mild, S2 moderate, and S3 severe, the corresponding CAP cut-off values for hepatic steatosis (S) were: <237-(248.0-267)-(268.0-279) - > 280.0 (dB/m).[15] The cut-off values for fibrosis (F) were > 10.4 kPa for F4, cirrhosis, F0 no fibrosis, F1 mild fibrosis, F2 moderate fibrosis, and F3 severe fibrosis, respectively. [16]

Statistical Analysis:

The data recorded was analyzed using version 23.0 of the statistical program for social sciences developed by SPSS Inc., based in Chicago, Illinois, USA. Parametric (normal) data were presented as the mean± deviations and ranges, while non-parametric (non-normally dispersed) variables were represented by the median and interquartile limit (IQR). Quantitative factors were represented as percentages and numerical values. The normality of the data was assessed using both Kolmogorov-Smirnov and Shapiro-Wilk tests.

A one-way assessment of variance (ANOVA) and the Kruskall-Wallis test is recommended when dealing with non-parametric data to compare the means of more than two groups. Post-Hoc test: Tukey's test was used to compare several variables simultaneously. When comparing groups containing qualitative data, Fischer's exact test was employed as a substitute for the Chi-square test when the average counts in any cell were below 5. The Pearson correlation coefficient (r) test assessed the degree of association among two values. Positive correlation: An increase in the independent variable leads to a corresponding increase in the dependent variable. Negative correlation: An increase in the separate variable results in a corresponding decrease in the dependent variable. The configuration of the resultant dots signifies the existence of correlation. A scatter chart is a graphical representation that displays the values of both variables on two perpendicular axes. The parameter's overall predictivity was assessed utilizing receiver operating characteristic (ROC) curves analysis. This analysis was also employed to determine the appropriate cut-off value for sensitivity and specificity.

3. Results

Table 1. Demographic data distribution among stud group

DEMOGRAPHIC DATA	TOTAL (N=100)
AGE (YEARS)	
RANGE	23-64
MEAN±SD	42.36±8.96
GENDER	
FEMALE	26 (26.0%)
MALE	74 (74.0%)

The age distribution was 23–64 years old, with a mean±SD of 42.36±8.96. There was a masculine predominance in terms of gender distribution, with 26 females and 74 men making up 74% and 26% of the total.

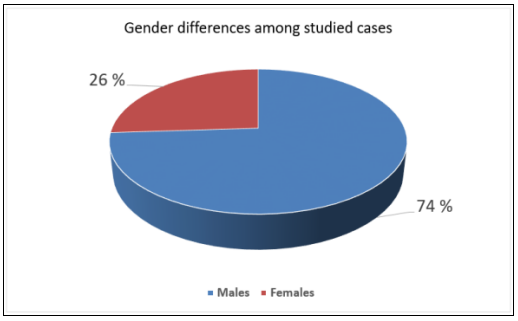

Figure 1. Pie chart gender distribution among study group.

Table 2. Anthropometric measurements distribution among stud group.

ANTHROPOMETRIC MEASUREMENTS	RANGE	MEAN±SD
HEIGHT (CM)	144-191.1	160.74±8.96
WEIGHT (KG)	66-130.1	95.42±13.07
WAIST CIRCUMFERENCE (W.C) (CM)	88-138	117.80±8.80
BODY MASS INDEX (BMI) (KG/M²)	23.94-53.28	37.60±5.71

The mean of Height (cm) was 160.74±8.96; weight was 95.42±13.07 kg; waist circumference was 117.80±8.80 cm; BMI was 37.60±5.71 kg/m2 of anthropometric measurements.

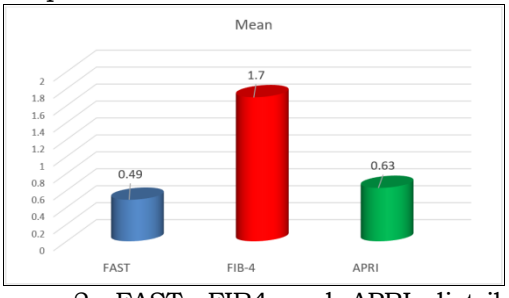

Figure 2. FAST, FIB4 and APRI distribution among study group.

Table 3. Relationship between the degree of fibrosis in the study group and the red cell distribution width and platelet ratio (RPR).

RPR	FIBROSIS LEVEL				F-TEST	P-VALUE
	F1 (n=47)	F2 (n=29)	F3 (n=16)	F4 (n=8)		
MEAN±SD	0.044±0.012	0.070±0.025	0.098±0.013	0.107±0.016		
RANGE	0.025 – 0.074	0.028-0.125	0.080-0.133	0.093-0.133	60.23	<0.001**

A one-way analysis of variance test was used to determine the mean±standard deviation, and a post-hoc test was used to compare groups multiple times. **p-value <0.001 is very significant in Tukey's test

Fibrosis F4 had the greatest mean RPR value (0.107±0.016), Fibrosis F3 (0.098±0.013), Fibrosis F2 (0.070±0.025), and F1 had the lowest value, at 0.044±0.012. A difference of statistical significance (P<0.001) was found between the groups according to an ANOVA test. There was a multiple significant difference between the fibrosis grades, according to Tukey's post hoc test.

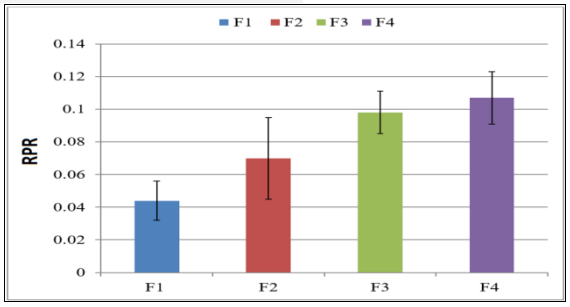

Figure 3. Red cell distribution width and platelet ratio (RPR) are correlated with the research group's degree of fibrosis.

Table 4. Association between fibrosis scores with degree of fibrosis among study group.

	FIBROSIS LEVEL				F-TEST	P-VALUE
	F1 (n=47)	F2 (n=29)	F3 (n=16)	F4 (n=8)		
FAST	0.38±0.16 0.14-0.81	0.50±0.17 0.02-0.80	0.66±0.13 0.52-0.84	0.74±0.07 (0.64-0.84)	48.44	<0.001**
FIB4	1.00±0.55 0.51-4.73	1.33±0.71 0.27-3.08	1.63±0.97 0.58-1.89	2.91±1.51 1.18-5.21	43.22	<0.001**
APRI	0.26±0.11 0.14-0.43	0.58±0.45 0.13-1.65	0.64±0.47 0.16-2.05	0.86±0.28 0.27-1.49	38.62	<0.001**

Tukey's test was used to make a multiple comparison between groups, and a one-way analysis of the variance was used to determine the mean±standard deviation. A p-value of less than 0.001 indicates a very significant result

The highest mean value of FAST, FIB-4 and APRI was recorded in F4, followed by F3, then F2 and lastly F1 recorded lower values of them with a group difference that is extremely statistically significant (P<0.01).

Table 5. Pearson's correlation coefficient (r) was used to examine the relationship between the red cell distribution width and platelet ratio (RPR) in the patient group based on anthropometric data.

PARAMETERS	RPR	
	r	p-value
AGE (YEARS)	0.019	0.848
HEIGHT (HT) (CM)	-0.024	0.807
WEIGHT (WT) (KG)	0.270	0.006*
WAIST CIRCUMFERENCE (CM)	0.198	0.047*
BODY MASS INDEX (BMI) (KG/M^2)	0.346	0.0004**
FASTING BLOOD GLUCOSE (FBG). (MG/DL)	-0.026	0.800
ALANINE TRANSAMINASE (U/L)	-0.045	0.655
ASPARTATE TRANSAMINASE (U/L)	-0.053	0.603
TOTAL BILIRUBIN (MG/DL)	-0.027	0.791
DIRECT BILIRUBIN (MG/DL)	-0.048	0.636
ALBUMIN (G/DL)	0.087	0.389
CREATININE (MG/DL)	0.111	0.269
TOTAL CHOLESTEROL (MG/DL)	-0.122	0.228
TRIGLYCERIDES. (MG/DL)	0.013	0.902
HIGH DENSITY LIPOPROTEIN (HDL) (MG/DL)	0.052	0.610
LOW DENSITY LIPOPROTEIN (LDL). (MG/DL)	-0.190	0.058

Using: p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS; Pearson's correlation coefficient (r)

RPR showed statistically significant positive correlations with weight (kg) (r=0.270; p=0.006), waist circumference (cm) (r=0.198; p=0.047), and BMI (kg/m2) (r=0.346; p=0.0004). Nonetheless, the p-value (p>0.05) indicates that there is little correlation between the other laboratory measurements.

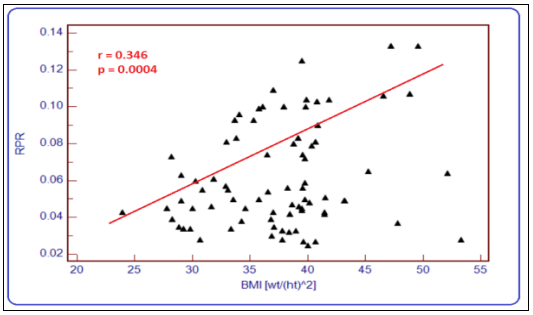

Figure 4. The red cell distribution width, platelet ratio (RPR), and body mass index (BMI) are plotted in a scatter plot.

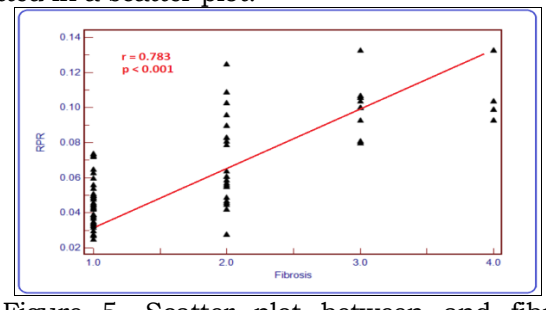

Figure 5. Scatter plot between and fibrosis classification.

Table 6. ROC curve for diagnostic receivers: an illustration Discrimination of fibrosis level using red cell distribution width to platelet ratio (RPR) performance.

GROUPS	CUT-OFF	SEN.%	SPE.%	PPV%	NPV%	AUC (95% C.I.)	P-VALUE
F1 VS. F2	>0.054	72.4%	82.9%	72.4%	83.0%	0.807 (0.700-0.889)	0.0001*
F1 VS. F3	>0.074	100%	100%	100%	100%	1.000 (0.943-1.000)	<0.001**
F1 VS. F4	>0.074	100%	100%	100%	100%	1.000 (0.934-1.000)	<0.001**
F 2 VS. F3	>0.079	100%	58.82%	57.1%	100%	0.800 (0.653-0.904)	0.003*
F 2 VS. F4	>0.090	100%	79.3%	54.5%	92.3%	0.879 (0.730-0.962)	0.0001**
F 3 VS. F4	>0.099	50.0%	31.25%	100%	76.2%	0.555 (0.340-0.755)	0.669

Sens.: Sensitivity; Spec.: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; AUD: Area Under the Curve. Cut-off values for RPR.

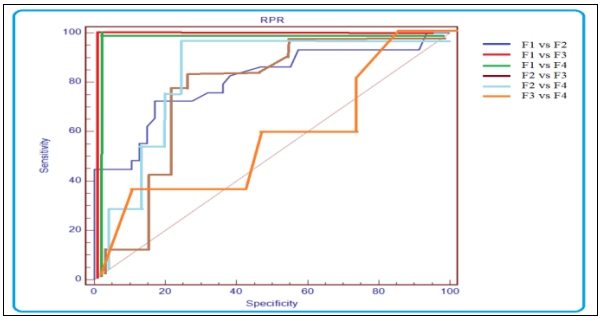

Figure 6. ROC curve for diagnostic Performance of RPR in Discrimination of fibrosis level.

Fibrosis F1 vs. F2: ROC curve was performed for red cell distribution width to platelet ratio (RPR) and demonstrated an area under the curve (AUC) of 0.807 (0.700-0.889) with P value 0.0001. The ideal threshold value for discrimination between F1 vs. F2 was >0.054 with sensitivity 72.4% and specificity 82.9%.

Fibrosis F1 vs. F3: ROC curve was performed for RPR and demonstrated an AUC 1.000 (0.943 - 1.000) with P value <0.001. The ideal threshold value for discrimination between F1 vs. F3 was >0.074 with sensitivity 100% and specificity 100%.

Fibrosis F1 vs. F4: ROC curve was performed for RPR and demonstrated an AUC of 1.000 (0.934 -1.000) with P value <0.001. The ideal threshold value for discrimination between F1 vs. F4 was >0.074 with sensitivity 100% and specificity 100%.

Fibrosis F2 vs. F3: ROC curve was performed for RPR and demonstrated an AUC of 0.800 (0.653-0.904) with P value 0.003. The ideal threshold value for discrimination between F2 vs. F3 was >0.079 with sensitivity 100% and specificity 58.8%.

Fibrosis F2 vs. F4: ROC curve was performed for RPR and demonstrated an AUC of 0.879 (0.730-0.962) with P value <0.001. The ideal threshold value for discrimination between F2 vs. F4 was >0.090 with sensitivity 100% and specificity 79.3%.

Fibrosis F3 vs. F4: ROC curve was performed for RPR and demonstrated an AUC of 0.555 (0.340-0.755) with P value = 0.669. The best cut off value for discrimination between F3 vs. F4 was >0.099 with sensitivity 50.0% and specificity 31.25%.

4. Discussion

Regarding associated comorbidities among studied cases, 31% of patients were complaining of hypertension and 48% of diabetes mellitus. This is in line with 17-18 studies.

In the current study, MAFLD patients had higher RPR, glucose, ALT, AST, total cholesterol, triglycerides, and LDL- cholesterol. The current study was by [19-20,17] studies.

In our studied cases, liver stiffness measurement (LSM) was 47%, 29%,16%, and 8% in F1, F2, F3, and F4, respectively. FibroCAP was 7%, 41%, and 52% in S1, S2, and S3, respectively. Compared to the current study, Tasci et al.'s 17 results were 45%,23%,10.8%,16.7%, and 4.2% in F0, F1, F2, F3, and F4, respectively.

Among enrolled patients, fibro scan AST (FAST), FIB4 and APRI were in the same line with.[21,20]

Our findings for APRI and FIB4 partially support the presence of liver fibrosis in patients. The optimal threshold for Lemoine et al.[22] Evaluated the efficacy of APRI and FIB-4 in differentiating between cirrhosis (F4) and severe fibrosis (≥ F2). APRI and FIB-4 demonstrated a notable increase in advanced liver fibrosis stages and served as reliable indicators of severe fibrosis in patients with chronic HBV infection. However, while examining the liver biopsy using histological analysis, they discovered that the APRI score was strongly associated with the severity of liver fibrosis and performed better than the FIB-4 score.

In contrast to recent research showing that RPR can detect substantial fibrosis, an Egyptian study by Gabr et al.,[23] The objective was to assess if RPR might find evidence of severe fibrosis in those with long-term hepatitis B, eliminating the need for the costly fibroscan procedure. There was no significant difference between the patient groups with minimal to mild liver fibrosis (F0-F1) and those with severe liver fibrosis (≥ F2) in terms of the calculated scores (RPR, FIB-4, and APRI).

4. Conclusion

The ratio of platelets to the red cell dispersion width, or RPR, is a quick and accessible diagnostic for estimating the severity of MAFLD disease. Due to its greater AUC, the RPR index outperforms FAST, FIB-4, and APRI when

predicting MAFLD. In patients with MAFLD, RPR can be employed as a noninvasive diagnostic marker to forecast severe fibrosis.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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