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Predictive value of biomarkers in steatohepatitis and fibrosis

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Abstract

Aim: Non-alcoholic fatty liver disease (NAFLD) has recently become a significant public health problem around the world, with a reported prevalence of 25%. In this study, we aimed to investigate the utility of biochemical and hematological markers in the progression from hepatosteatosis to fibrosis and to examine their superiority to each other by comparing them with pathological scoring parameters.

Materials and Methods: Pathological results of patients who underwent liver biopsy for different indications were reviewed retrospectively.Of these, 120 patients with fatty liver were selected and their biopsy specimens were re-evaluated according to the NAFLD Activity Score (NAS). The relationship between pathological scores and serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST to platelet ratio index (APRI), red blood cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), RDW to platelet ratio (RPR), and gamma-glutamyl transpeptidase (GGT), RDW to platelet ratio (RPR), and gamma-glutamyl transpeptidase (GGT) was analyzed.

Results: The results indicated that ALT, APRI, and GGT were significant predictors of nonalcoholic steatohepatitis (NASH), while GGT, APRI, and RPR were significant predictors of fibrosis. Additionally, ROC analysis confirmed the significant predictive value of APRI, RPR, and GGT in the diagnosis of fibrosis.

Conclusion: Based on these results, we consider that GGT and APRI are better predictors than other biomarkers.

Introduction

Non-alcoholic fatty liver disease (NAFLD) has recently become a significant public health problem around the world. Its worldwide prevalence is considered to be around 25% [1]. In a study conducted in Turkey, its prevalence was found to range between 48.3-60.1% [2]. Approximately 7-30% of NAFLD patients progress to nonalcoholic steatohepatitis (NASH) and 10-20% of them progress to liver cirrhosis [3-5].

Triglyceride accumulation in the hepatocytes is termed 'fatty degeneration' if the ratio is between 5-50% and 'fatty liver' if it is above 50%. Additionally, it is termed 'steatohepatitis' in the coexistence of hepatocellular ballooning and inflammation. Progression of inflammation leads to liver fibrosis and cirrhosis. Liver fibrosis is the most important indicator of mortality in NAFLD. Progression to fibrosis can be prevented or delayed through continuous follow-up and prompt treatment [6,7].

Liver biopsy remains the gold standard in the evaluation of the progression from hepatosteatosis to fibrosis. However, its invasive nature, increased costs, and risks of hypotension, syncope, pain, bleeding, hemothorax, and potentially fatal complications has led to the search of new evaluation criteria [8]. On the other hand, the lack of adequate noninvasive tests in the follow-up is another important problem [9]. For these reasons, a wide range of biochemical and hematological parameters have been examined in many studies for both the diagnosis and follow-up of NAFLD, including neutrophil-to-lymphocyte ratio (NLR), red blood cell distribution width (RDW), RDW to platelet ratio (RPR), aspartate aminotransferase (AST) to platelet ratio index (APRI), and alanine aminotransferase (ALT) [7,10-15].

In this study, we aimed to investigate the utility of biochemical and hematological markers in the progression from hepatosteatosis to fibrosis and to examine their superiority to each other by comparing them with pathological scoring parameters.

We also aimed to explore the utility of these parameters

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in clinical practice by analyzing their sensitivity and specificity.

Materials and Methods

The retrospective study reviewed the pathological results of patients who underwent liver biopsy for different indications in two different tertiary hospitals between 2010 and 2020. Considering the exclusion criteria among those who underwent liver biopsy, 120 patients with fatty liver were selected and these patients formed the sample of the study.

Exclusion criteria were as follows: active infections, ongoing treatments that could affect the neutrophil and leukocyte levels, kidney disease, malignancies, rheumatic diseases and use of anti-inflammatory drugs for these diseases, use of drugs that could affect the bone marrow, benign or malignant hematological conditions and steroid use.

Data on liver function tests, complete blood count (CBC) parameters, drugs, comorbidities, and demographic characteristics that were recorded on the date of biopsy were retrieved from the hospital database.

Hematoxylin and eosin (H&E) stained liver samples were re-examined for liver fat rate and presence of lobular inflammation and ballooning degeneration. Presence of fibrosis was evaluated using Masson's trichrome stain. NASH was graded according to the total score (0-2, 3-4, and 5-8). Based on NAS scores, the pathological findings were classified as occult, suspicious, and steatohepatitis. Fibrosis was graded on a 5-point scale (0 to 4). Stage 4 indicates advanced fibrosis and cirrhosis in the liver [16].

Biochemical measurements were performed using the enzymatic method on a Beckman Coulter AU5800 autoanalyzer with genuine system reagents. CBC parameters were analyzed using a Sysmex XN-9000 Hematology Autoanalyzer.

Serum levels of ALT, AST, APRI, RDW, RPR, NLR, and GGT that were assessed prior to biopsy were retrieved from hospital database. The relationship between biochemical and hematological parameters and pathological scores was analyzed. RPR was calculated using the following formula: RDWx100/PLT (109/L) [17].

Ethical approval for this study was obtained from Karadeniz Technical University, Health Sciences Non-Interventional Clinical Research Ethics Committee (Date: 15.04. 2021, Decision Number: 2021/98).

Statistical analysis

Data were analyzed using SPSS for Windows version 23.0 (Product ID: 00330-53730-07352-AAOEM). Quantitative datas were expressed as median (25^{th}-75^{th} percentile) and qualitative datas were expressed as number (n) and percentages (%). The main hypothesis of the study is that some identified biomarkers (APRI, RPR, ALT, GGT, RDW, NLR and CRP) are associated with steatohepatitis and fibrosis and can be used predictively in making these diagnoses. Normal distribution of continuous variables was assessed using Kolmogorov-Smirnov test. Since the biomarker levels showed non-normal distribution, the relationship between biomarkers and steatohepatitis and fibrosis was compared using the Kruskal-Wallis test followed by the post-hoc Bonferroni test. Correlations between biomarkers and steatohepatitis and fibrosis were determined using Spearman's Correlation Coefficient. Predictive value of biomarkers in detecting steatohepatitis and fibrosis were analyzed using Receiver Operating Characteristics (ROC) curve analysis. In the presence of significant cutoff points, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of these cutoff points were calculated. A p value of <0.05 was considered significant.

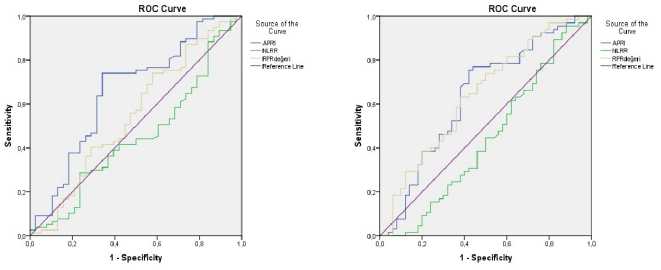
Results

The 120 patients comprised 62 (51.7%) men and 58 (48.3%) women with a mean age of 46 (range, 33.3-58.0) years. Type 2 diabetes mellitus (T2DM) was present in 17.4% (n=20) and hypertension was present in 23% (n=27) (Table 1).

Biopsy results indicated no fibrosis in 54 (45.0%) patients, while they showed pericinusoidal or periportal fibrosis in 28 (23.3%), pericinusoidal and portal/periportal fibrosis in 13(10.8%), bridging fibrosis in 20(16.7%), and cirrhosis in 5(4.2%) patients. Additionally, the results showed no steatohepatitis in 39 (32.5%), suspicious steatohepatitis in 52(43.3%), and steatohepatitis in 29 (24.2%) patients (Table 2).

The APRI and ALT values were significantly higher in patients with steatohepatitis compared to patients without steatohepatitis (p=0.014 and p=0.007, respectively). Moreover, the RPR and GGT values were statistically significantly higher in patients with Stage 4 fibrosis compared to patients without fibrosis (p=0.027 and p=0.039, respectively). No significant difference was found for the remaining biomarkers (Table 3).

Correlation analysis indicated a significant positive correlation between APRI, ALT, and GGT levels and the severity of steatohepatitis and between APRI and GGT levels and the severity of fibrosis (Table 4).



	AUC	Cut-off	Sensitivite	Spesifite	PPD	NPD
Steatohepatit						
APRI	0,644	0,525	74,4	65,8	81,7	55,6
ALT	0,653	37,50	73,1	42,1	72,2	43,2
GGT	0,604	33,50	76,0	47,2	75,0	48,6
Fibrozis						
APRI	0,622	0,514	77,3	56,0	69,9	65,1
RPR	0,623	0,0547	78,5	42,0	63,7	60,0
GGT	0,604	30,500	77,8	37,5	62,0	56,3

AUC: Area under the ROC curve, APRI: AST to platelet ratio index, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transpeptidase, RPR: RDW to platelet ratio.

Figure 1. Predictive values of biomarkers in the diagnosis of steatohepatitis.

Table 1. Demographic and clinical characteristics.

	Patients	
	n	%
Age (years)	46.0 (33.3-58.0)	
Gender (%)		
Female	58	48.3
Male	62	51.7
BMI (kg/m^2)	26.8 (24.7-32.8)	
Comorbidities (%)		
T2DM	20	17.4
Hypertension	27	23.5
Laboratory parameters (median, 25th-75th percentile)		
Glucose	102.0 (90.0-126.0)	
ALT(U/L)	56.5 (34.0-108.3)	
AST(U/L)	43.0 (33.3-67.8)	
Triglyceride	134.0 (88.8-190.0)	
Cholesterol	187.0 (166.0-210.8)	
HDL	44.0 (38.0-56.0)	
LDL	19.0 (96.0-141.0)	
GGT(U/L)	51.0 (27.0-108.0)	
PT	12.3 (11.6-13.3)	
ALP	89.0 (70.0-118.0)	
LDH	228.5 (192.8-272.3)	
Uric acid	5.3 (4.4-6.2)	
Fe	81.0 (62.0-115.0)	
FeBC	352.0 (285.3-380.3)	
CRP	0.07 (0.0-0.5)	
Sedimentation	11.0 (5.0-41.0)	
WBC	6.9 (5.7-8.9)	
Neutrophil	3.8 (3.1-5.2)	
Lymphocyte	2.30 (1.80-2.89)	
Platelet	213.5 (162.8-261.5)	
HBG	13.9 (12.5-15.3)	
HCT	41.2 (37.7-45.4)	
MCV	87.5 (84.0-90.5)	
RDW(%)	13.3 (12.9-14.3)	
PDW	16.1 (13.1-16.8)	
APRI	0.6 (0.4-1.0)	
NLR	1.8 (1.4-2.3)	
RPR	0.06 (0.05-0.08)	

T2DM: Type 2 diabetes mellitus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, GGT: Gamma-glutamyl transpeptidase; PLT: Platelet count, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, WBC: White blood cell count, HBG: Hemoglobin, HCT: Hydrochlorothiazide, MCV: Mean corpuscular volume, RDW: Red blood cell distribution width, PDW: Platelet distribution width, APRI: AST to platelet ratio index, NLR: Neutrophil-to-lymphocyte ratio, RPR: RDW to platelet ratio.

In the ROC analysis conducted to evaluate the predictive value of biomarkers for the diagnosis of steatohepatitis, the area under the ROC curve (AUC) values for APRI, ALT, and GGT were 0.644, 0.653, and 0.604, respectively.

Table 2. Biopsy results.

	n	%
Fibrosis		
None	54	45.0
Stage 1	28	23.3
Stage 2	13	10.8
Stage 3	20	16.7
Stage 4	5	4.2
Steatohepatitis		
None	39	32.5
Suspicious	52	43.3
Steatohepatitis	29	24.2

In the ROC analysis conducted to evaluate the predictive value of biomarkers for fibrosis, the AUC values for APRI, RPR, and GGT were 0.622, 0.623, and 0.604, respectively (Figure 1).

Discussion

Liver biopsy is the gold standard in the diagnosis of fibrosis and hepatosteatosis. In patients with NASH, there is no difference between the absence of fibrosis and the presence of minimal fibrosis, but the detection of patients with severe fibrosis is highly important since they require a different treatment approach [18]. In the literature, liver cirrhosis has been blamed for approximately 9.7% of deaths [19].

In the present study, we determined the correlations between biomarkers that have been shown to be predictive in previous studies and the severity of steatohepatitis and fibrosis based on pathological results. We consider that the development of a simple, practical hematological parameter will bring awareness to liver cirrhosis in the early period and will reduce associated deaths. Nonetheless, although there are many studies conducted on this subject, there is no full consensus in the literature [7,9-15].

In the present study, we evaluated the predictive value of RDW, RPR, ALT, APRI, and GGT in the diagnosis of steatohepatitis and fibrosis based on pathological results, and we also investigated their sensitivity and specificity values. Among these, APRI and ALT, which are biomarkers of steatohepatitis, showed a significant difference. This finding was consistent with the findings of previous studies conducted with ALT [20]. APRI, on the other hand, has been accepted as a biomarker of fibrosis in previous studies [21]. In our study, RPR, GGT, RDW, NLR, and CRP showed no significant difference in the diagnosis of steatohepatitis. Additionally, APRI, GGT, and ALT had no significant predictive value for the diagnosis of steatohepatitis in ROC analysis.

In our study, APRI showed a sensitivity of 74.4% at a cutoff value of 0.525 for the diagnosis of steatohepatitis and a sensitivity of 77.3% at a cutoff value of 0.514 for the diagnosis of fibrosis. Although supporting findings have been reported in other studies, some studies have suggested that APRI is superior to other biomarkers [7,10-12.22,23].

Table 3. Comparison of biomarkers according to the stages of steatohepatitis and fibrosis.

	Steatohepatitis				Fibrosis					
	None	Suspicious	Steatohepatitis	p	None	Stage 1	Stage 2	Stage 3	Stage 4	p
APRI	0.48	0.67	0.83	**0.014***	0.49	0.60	0.63	0.86	0.76	0.058
	(0.34-0.78)	(0.40-1.13)	(0.56-1.21)		(0.34-0.86)	(0.39-1.17)	(0.46-1.15)	(0.61-1.19)	(0.67-1.79)	
RPR	0.06	0.07	0.06	0.136	0.06	0.06	0.06	0.08	0.09	**0.027****
	(0.05-0.08)	(0.06-0.09)	(0.05-0.08)		(0.05-0.07)	(0.05-0.08)	(0.06-0.07)	(0.05-0.10)	(0.08-0.12)	
ALT	45.00	56.0	93.0	**0.007***	52.00	51.00	72.00	65.50	38.00	0.868
	(26.75-76.25)	(33.0-109.0)	(47.0-146.0)		(28.75-123.50)	(31.25-97.50)	(34.00-110.50)	(47.75-80.00)	(35.50-100.00)	
GGT	38.50	46.0	77.50	0.114	40.50	54.00	44.00	78.00	120.00	**0.039****
	(24.00-105.25)	(29.0-115.0)	(40.50-112.75)		(24.00-97.50)	(30.00-103.00)	(27.00-97.50)	(37.00-123.00)	(82.75-501.50)	
RDW	14.05	13.20	13.35	0.171	13.30	13.40	12.90	13.50	14.30	0.087
	(13.00-14.75)	(12.80-14.30)	(12.98-14.12)		(12.98-14.40)	(12.80-14.30)	(12.25-13.30)	(13.13-14.75)	(13.15-16.55)	
NLR	1.86	1.85	1.63	0.583	1.86	1.92	1.61	1.40	2.01	0.152
	(1.43-2.32)	(1.31-2.33)	(1.32-2.16)		(1.36-2.45)	(1.63-2.28)	(1.15-1.89)	(1.15-2.14)	(1.37-16.55)	
CRP	0.31	0.02	0.0	0.171	0.03	0.21	0.15	0.00	2.01	0.287
	(0.00-0.66)	(0.00-0.38)	(0.0-0.37)		(0.00-0.44)	(0.00-0.66)	(0.00-0.36)	(0.00-0.36)	(1.37-2.69)	

*None vs. steatohepatitis, **None vs. cirrhosis
APRI: AST to platelet ratio index, RPR: RDW to platelet ratio, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transpeptidase; RDW: Red blood cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein.

Table 4. Correlations between biomarkers and the severity of steatohepatitis and fibrosis.

	Steatohepatitis		Fibrosis	
	r	p	r	p
APRI	**0.267**	**0.004**	**0.271**	**0.003**
RPR	-0.16	0.869	0.272	0.003
ALT	**0.288**	**0.002**	0.067	0.474
GGT	**0.198**	**0.037**	**0.269**	**0.004**
RDW	-0.121	0.197	0.039	0.682
NLR	-0.095	0.311	-0.139	0.137
CRP	-0.164	0.074	0.057	0.539

APRI: AST to platelet ratio index, RPR: RDW to platelet ratio, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transpeptidase; RDW: Red blood cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein.

Taken together, the findings of other studies and our study indicate that APRI can be a useful parameter for early diagnosis and treatment of fibrosis and steatohepatitis.

However, another study compared APRI with elestography and suggested that elestography could be superior to APRI in the diagnosis of fibrosis [23]. APRI and elestography can be used together in decision-making processes. Another study argued that APRI may provide limited information for the diagnosis of fibrosis in patients with chronic hepatitis B virus (HBV) infection [24].

Red blood cell distribution width (RDW) to platelet ratio (RPR) has been shown to be a potential biomarker in many different areas [12,17,25-27]. In our study, although RPR showed a significant predictive value for fibrosis, it showed no significant correlation. These findings implicate that RPR could be used in the diagnosis of fibrosis, while pathological results demonstrated that it may not be a good predictive marker for NASH. This finding could be attributed to the greater changes in platelet counts in fibrosis when compared to NASH [28,29].

The use of RDW as an extrahepatic biomarker has been shown in numerous studies [12,30-32]. Moreover, the relationship between RDW and mortality-related factors has been explained via inflammation and oxidative stress [33,34]. Nevertheless, although RDW has been shown to increase in the presence of liver cirrhosis, it is not clear as to whether RDW can be used a biomarker of the stages of liver cirrhosis [35,36]. Some other studies suggested that elevated RDW values lead to increased risk of fibrosis and that RDW can be accepted as a prognostic index [30,37].

In our study, RDW had no significant predictive value in the diagnosis of fibrosis or NASH. Considering that other studies have used more clinical scores, it can be argued that RDW is clinically significant, but pathologically insignificant. Regardless, we consider that larger pathological studies are needed on this subject [30,35].

It is commonly known that pathological results may not always correlate with the clinical course of the disease. In addition, in order to show necroinflammation, more extensive research should be conducted to address how reasonable it would be to accept RDW, which is affected by many different clinical factors, as a prognostic factor [31]. We consider that excluding the patients with malignancies and active infections in our study and the fact that these two exclusion criteria are not always applied in other studies may have affected the absence of a correlation between RDW and NASH [38,39].

On the other hand, GGT was significantly associated with the pathological results related to steatohepatitis and fibrosis in our study. Although some studies have provided opposite results, many other studies suggested that GGT may be a predictive marker of hepatic fibrosis [40,41]. Additionally, GGT has been shown to be a good indicator of NASH as well [42,43]. Our findings supported these clinical findings by providing pathological evidence.

Conclusion

Biomarker studies typically aim to obtain pathological results with less time, effort, and cost. Accordingly, our results indicated that ALT, APRI, and GGT can be predictive biomarkers for NASH and that GGT, APRI, and RPR can be predictive biomarkers for fibrosis. As consistent with the literature, the ROC curve analysis also showed that APRI, RPR, and GGT are significant predictors of fibrosis. Taken together, these findings suggest that GGT and APRI are better predictors than other biomarkers.

Pathological results may not always correlate with the clinical course of the disease. Nevertheless, considering that predictive markers are associated with necroinflammation, it is tempting to consider that pathological indicators may provide more substantial information. Based on these findings, we suggest that evaluating clinical and pathological results together could be a useful approach in the determination of predictive values of biomarkers.

Ethical approval

Ethical approval for this study was obtained from Karadeniz Technical University, Health Sciences Non-Interventional Clinical Research Ethics Committee (Date: 15.04. 2021, Decision Number: 2021/98).

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