International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2025; 8(3): 49-57
Received: 25-06-2025
Accepted: 29-07-2025

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Evaluation of relation of serum reelin and stages of liver fibrosis in a sample of Iraqi patients with chronic liver disease

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DOI: https://www.doi.org/10.33545/pathol.2025.v8.i3a.2093

Abstract

Background: Chronic liver diseases are characterized by progressive deterioration of liver function, leading to fibrosis and cirrhosis through persistent inflammation, hepatocellular injury, and repair. These changes result in nodular regeneration, vascular remodeling, angiogenesis, and extracellular matrix (ECM) deposition. Reelin, an ECM glycoprotein previously implicated in neurological disorders, may also play a role in hepatic fibrogenesis. This study investigates serum reelin levels as a potential biomarker for different stages of hepatic fibrosis.

Aim: To evaluate serum reelin levels in chronic liver disease patients compared to healthy controls, and to assess its correlation with fibrosis stage.

Methods: A case-control study was conducted from February to August 2022, including 84 participants: 56 patients with chronic liver disease and 28 age-matched healthy controls. Patients were categorized by Fibroscan into advanced fibrosis (AF; F3/F4) and non-advanced fibrosis (NAF; F0-F2) groups. Serum AST, ALT, bilirubin, and ALP were measured using an automated chemistry analyzer, while serum reelin was quantified by ELISA.

Results: Median serum reelin was significantly higher in AF patients (14.4 ng/mL, Q1=5.05, Q3=33.29) than in NAF patients (1.32 ng/mL, Q1=0.78, Q3=1.98; $p<0.001$) and controls (1.34 ng/mL, Q1=1.05, Q3=1.64; P=0.001). Weak correlations were observed between reelin and liver function parameters, except for bilirubin in AF (P=0.024) and ALP in NAF (P=0.0002).

Conclusion: Serum reelin demonstrates high diagnostic potential in distinguishing advanced hepatic fibrosis from non-advanced fibrosis and healthy individuals but shows limited utility in differentiating individual non-advanced stages due to minimal fibrosis progression.

Keywords: Serum reelin, stages, liver, fibrosis, chronic, liver, disease

Introduction

The liver, the largest internal organ, weighs 1-1.5 kg and constitutes 1.5-2.5% of lean body mass. Its size and shape vary with body habitus, and it occupies the right upper quadrant, extending variably into the left upper quadrant, secured by ligamentous attachments to adjacent structures. The liver receives a dual blood supply: ~20% oxygen-rich blood from the hepatic artery and ~80% nutrient-rich blood from the portal vein draining the gastrointestinal tract and spleen [1, 2]. Functionally, the liver plays a central role in metabolism, protein synthesis, detoxification, bilirubin metabolism, lipid processing, bile excretion, glycogen storage, and immune defense. These functions are mediated by hepatocytes, cholangiocytes, Kupffer cells, endothelial cells, and portal fibroblasts [3]. Liver disease, resulting from diverse etiologies, disrupts these processes, with chronic liver disease (CLD) defined as progressive hepatic dysfunction persisting for over six months [4, 5]. Major causes of CLD include alcohol-associated liver disease [1], non-alcoholic fatty liver disease (NAFLD), which has a global prevalence of 25% and is strongly linked to metabolic syndrome [6], viral hepatitis (HBV, HCV) [7], autoimmune disorders such as primary biliary cholangitis, primary sclerosing cholangitis, and autoimmune hepatitis [8,9], and genetic disorders including hemochromatosis, Wilson disease, and α1-antitrypsin deficiency [10]. Globally, NAFLD accounts for 59% of CLD cases, HBV for 29%, HCV for 9%, and alcohol for 2% [11]. In Iraq, HBV prevalence was 1.98% in 2019, while HCV prevalence fluctuated from 1.2% in 1990 to 1.09% in 2019 [12]. Cirrhosis represents the end stage of CLD, characterized by architectural distortion, nodule formation, vascular remodeling, and extracellular matrix deposition [8].

Fibrosis progression results from chronic injury and activation of hepatic stellate cells (HSCs), which transform into myofibroblasts producing collagen [13]. This process involves interactions with liver progenitor cells, sinusoidal endothelial cells, and ductular reaction (DR) cells [13, 14]. Non-invasive fibrosis assessment tools, such as Fibroscan and serum biomarkers, aim to reduce reliance on liver biopsy. Among these, Reelin a 420 kDa extracellular glycoprotein has emerged as a potential marker. Originally recognized for its role in neuronal migration via VLDLR and ApoER2 receptor pathways involving Dab1 phosphorylation [14, 15], reelin is also expressed in HSCs and upregulated in fibrotic liver tissue [14]. Evidence suggests reelin may influence HSC migration, DR activation, and hepatic progenitor cell regulation, thereby contributing to fibrogenesis [14]. Elevated circulating reelin levels have been reported in cirrhosis, suggesting potential diagnostic value for advanced fibrosis [14]. This study evaluates serum reelin levels in CLD patients versus healthy controls and investigates correlations with fibrosis stage, aiming to clarify its role as a non-invasive biomarker for hepatic fibrosis.

Methods

This case-control study was conducted from February to August 2022 at the Gastroenterology and Hepatology Center, Ghazi Al-Hariri Surgical Specialties Hospital, Baghdad Medical City, and Merjan Teaching Hospital, Babylon. Eighty-four participants were enrolled: 56 patients with chronic liver disease (CLD) and 28 age-matched apparently healthy controls. Patients were classified using transient elastography (Fibroscan) into advanced fibrosis (AF; F3/F4) and non-advanced fibrosis (NAF; F0-F2) groups. Inclusion criteria included CLD patients and healthy controls. Exclusion criteria were gastrointestinal malignancies, neuropsychiatric disorders, eye diseases, and use of psychotropic medications. Ethical approval was obtained from the Iraqi Board for Medical Specializations and the Ministry of Health, with informed consent from participants. Baseline data, anthropometric measurements, and BMI classification (WHO) were recorded. Sample collection: Five mL of venous blood was drawn, allowed to clot, centrifuged, and serum aliquoted. Aliquot 1 was analyzed immediately for AST, ALT, ALP, and bilirubin using an Abbott Architect c4000 analyzer. Aliquot 2 was stored at −20°C for serum reelin determination by ELISA (Bioassay, China). Reelin assay: A sandwich ELISA was performed with pre-coated reelin antibodies, biotinylated detection antibody, and streptavidin-HRP, followed by substrate addition and absorbance measurement at 450 nm. Concentrations were calculated using a standard curve.

Liver function tests:-

- **Bilirubin:** Diazo method, absorbance at 548 nm.
- **AST/ALT:** NADH oxidation monitored at 340 nm.
- **ALP:** Hydrolysis of p-nitrophenyl phosphate, absorbance at 404 nm.
- **Statistical analysis:** Data were analyzed using Excel 2019 and GraphPad Prism 8. ANOVA or Kruskal-Wallis tests with Dunn's post hoc were applied. Chi-square tested categorical variables. Spearman correlation assessed associations, with Cohen's criteria for effect size. Receiver operating characteristic (ROC) analysis evaluated diagnostic performance of reelin. A *p*-value <0.05 was considered statistically significant.

Results

The analysis of fibro- scan revealed 34 patients belong to the F0, F1and F2 group comprising no to minimal fibrosis is considered as non-advanced fibrotic liver disease (NAF), 22 out of 56 patients in the F3 and F3/F4, F4 which is considered as Advanced fibrotic liver disease (AF), The most frequently observed type of chronic liver disease within the patients was Hepatitis B (n=25, 44.64%) followed by NAFLD 18 (32.14%). As shown in Table 1.

Table 1: Fibro scan staging of chronic liver diseased participants

Variable	Category	Frequency (n)	Relative Frequency (%)
Fibroscan (N=56)	F0/F1	28	50.00
	F2	6	10.71
	F3	9	12.50
	F3/F4	2	3.57
	F4	11	19.64
Type of Chronic Liver Disease (N=56)	Hepatitis C	6	10.71
	Hepatitis B	25	44.64
	AIH	5	8.93
	Other	2	3.57
	NAFLD	18	32.14

Mean ± SD of age for the patients was 42.72±14.03, and those aged (40-49) years made up the largest demographic (26.79%, with n=15), after that the age group of 30-39 years (n=13, 23.21%). Patients with liver disease tended to be non-significantly older than the 28 healthy subjects in the control group who had mean age of (40.29±11.19) years, p=0.43 with median age of 40 and standard error of the mean 2.1. Table 3-3 contain summary for the data. There was a mean age of (48.318±15.41) for patients with AF which was significantly higher than that for NAF age (39.10±11.95). Female number was equal to male in AF group both with 11 participants (50%). While in NAF group male gender was 22 (64.7%) and female comprised 12 (35.3%). However, there was no statistically significant difference among the groups regarding gender distribution χ^2=4.046, P=0.1323. Within control group 39.3% (11) were male while 60.7% (N=17) were female. As in Table 2.

Table 2: Age distribution and comparison among study groups, gender distribution among study groups.

Age Group (years)	Patients N=56, N	Patients %	Group	N	Mean ± SD (years)	Statistical test	P-Value
≤19	2	3.57					
20-29	11	19.64					
30-39	13	23.21					
40-49	15	26.79					
50-59	9	16.07					
≥60	6	10.71					
			Patients	56	42.72±14.03	t=1.98[a]	0.43
			Controls	28	40.29±11.19		
			AF	22	48.32±15.41	F=3.9[b], R^2=0.29	0.0251
			NAF	34	39.10±11.95		
			Controls	28	40.29±11.19		

Comparison	Mean Difference	95% CI of Difference	Adjusted p-value
AF vs. NAF	9.2	0.92 to 18	0.0259
AF vs. Control	8.0	−0.61 to 17	0.0741
NAF vs. Control	−1.2	−8.9 to 6.6	0.9290

Group	Female n (%)	Male n (%)	Total n (%)	Chi-squared	P-Value
AF	11 (50.0%)	11 (50.0%)	22 (26.2%)	4.046	0.1323
Control	17 (60.7%)	11 (39.3%)	28 (33.3%)		
NAF	12 (35.3%)	22 (64.7%)	34 (40.5%)		
Total	40 (47.6%)	44 (52.4%)	84 (100%)		

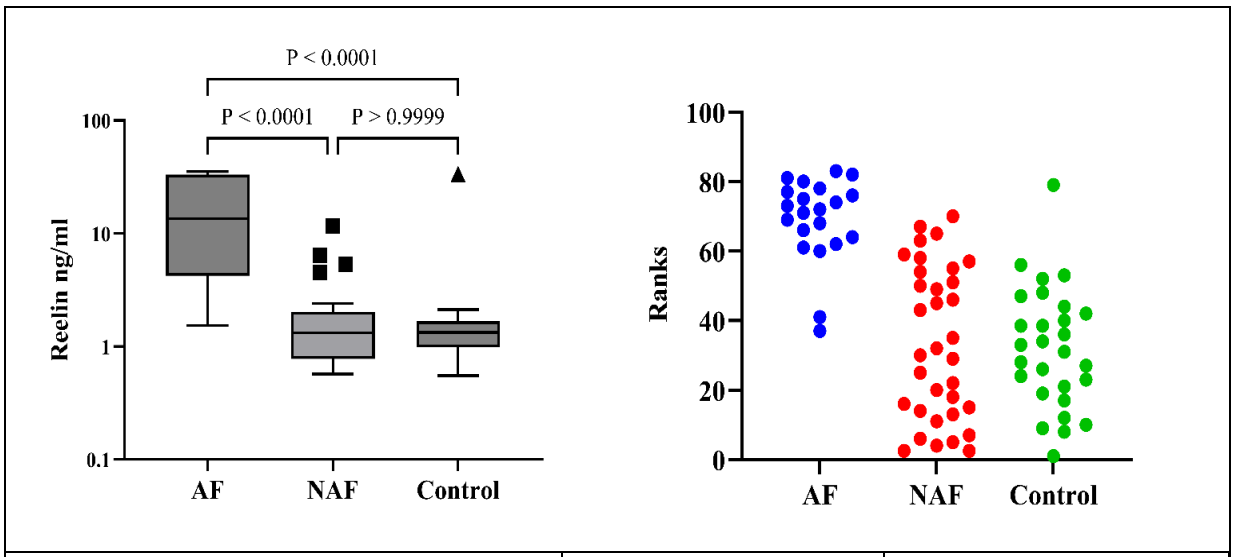
The BMI was classified according to the WHO scale where the distribution is as follows (<18.5-underweight), (18.5-24.9-normal), (25-29.9 overweight), (25-29.9 over weight), (30- 34.9 class I obesity), (35.0-39.9 class II obesity), (above 40 class III obesity). The mean BMI for patients was 28.68±5.94 and the majority of the patients were in the overweight group N=23 (41.07%) The mean BMI for control group was 23.64±1.41 and the majority of the control subjects were in the Pre-obesity BMI category of Pre-obesity N=17 (60.71%), as shown in Table 3. The mean of body mass index (BMI) among those with AF was (29.17±7.04kg/m2). The mean of body mass index for NAF was (28.36±5.20kg/m2). While, the mean body mass index for the control group was (23.64±1.41kg/m2). There were statistically significant differences between the groups as revealed by ANOVA result {F (2, 81)=9.85, p<.001}. The statistics of pair-wise comparison showed that the mean BMI of those with AF (M=29.17±SD=7.04 kg/m2) was statistically greater than that of those of control (M=23.64±SD=1.41kg/m2). NAF had a significantly higher mean body mass index BMI (M=28.36±SD=5.20kg/m2) when compared to control group (M=23.64± SD=1.41 kg/m^2), p<0.001. Table 3 displays the means and variances.

Table 3: Summery comparison table of BMI between groups

	BMI categories	Patient, n=56	Control, n=28	χ^2	P
BMI Categories Kg/m2	≤18.5	1 (1.79%)	0 (0.00%)	29.878	<.001
	(18.5- 22.9)	5 (8.93%)	8 (28.57%)		
	(23- 24.9)	10 (17.86%)	17 (60.71%)		
	(25- 29.9)	23 (41.07%)	3 (10.71%)		
	≥ 30	17 (30.36%)	0 (0.00%)		
	Total	56 (100%)	28 (100%)		
	Groups	Mean ± SD		T	P
BMI Kg/m2	Patients, N=56	28.68±5.94		6.019	<.001
	Control, N=28	23.64±1.41			
	Groups	Mean ± SD		F	P
	AF N=22	29.175±7.0413		9.853	<.001
	NAF N=34	28.359±5.1962			
	Control N=22	23.639±1.4088			

Turkey's multiple comparisons test			
Combination	Mean Diff.	95.00% CI of diff.	Adjusted P Value
AF vs. NAF	0.82	-2.4 to 4.1	0.8192
AF vs. Control	5.5	2.2 to 8.9	0.0005
NAF vs. Control	4.7	1.7 to 7.7	0.0010

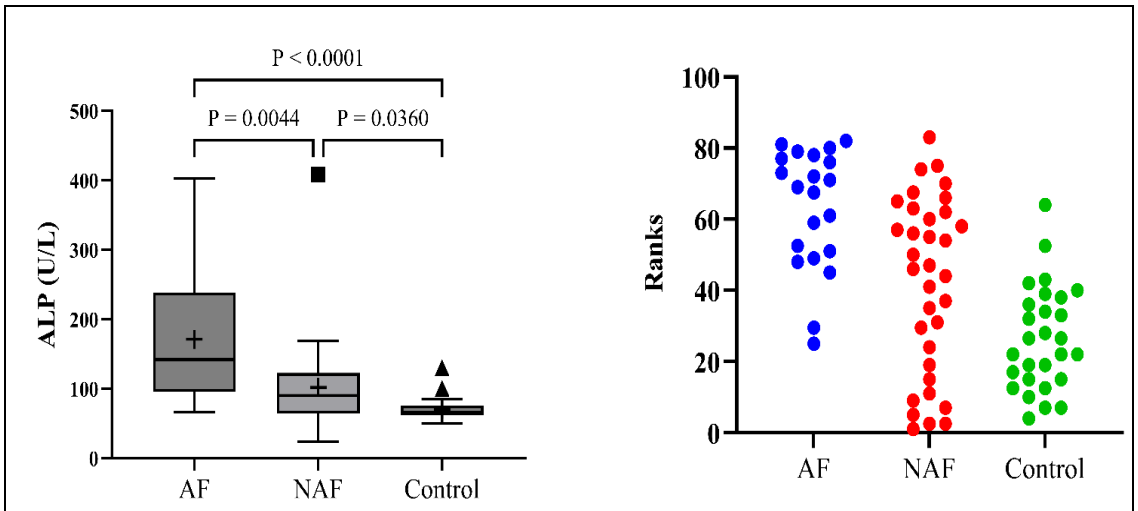
For AF, the reelin had a mean of (17.29±13.37ng/ml) and median=(14.04 ng/ml). For NAF, reelin had a mean of (1.96±2.17 ng/ml), median=(1.32ng/ml). For control, reelin had a mean of (2.46±6.08 ng/ml), median=(1.33 ng/ml). To determine whether there was a significant difference in reelin levels between the groups, a Kruskal-Wallis test was carried out. The results were significant, as shown in Figure 1, demonstrating that there are significant differences between the groups' mean rankings. This is indicated by the fact that the P value was less than 0.000001. After conducting a post-hoc analysis with the Dunn method for pairwise comparison, it was found that the mean rank of reelin for the AF group, which was 69.73, was significantly higher than that of the NAF group, which was 33.50, and the control group, which was 32.04.



Dunn's multiple comparisons test	Mean rank diff.	Adjusted P-Value
AF vs. NAF	36	<0.0001
AF vs. Control	37	<0.0001
NAF vs. Control	1.5	>0.9999

Fig 1: Mean ranks of serum reelin in patient's subgroups and control

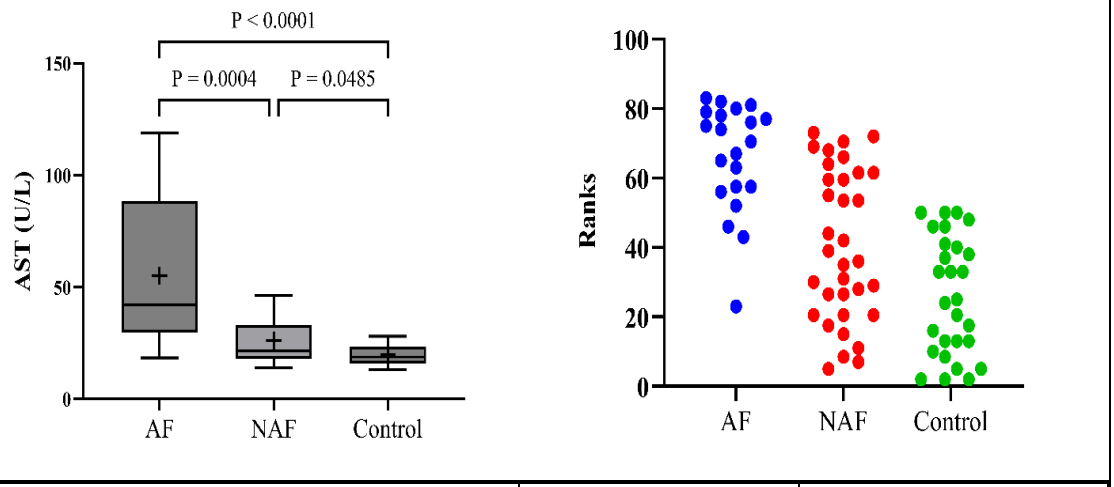
For AF, ALP had a mean of (165.57±99.24 u/l), median=(141.50 u/l). For NAF, ALP had a mean of (101.79±65.07u/l), median=(90.65 u/l). For control, ALP had a mean of (70.18±15.99 u/l), median=(66.50 u/l). A significant Kruskal-Wallis test result of (p<.001) suggests that there are significant differences in ALP between the groups. The mean rank ALP for AF=61.34 was significantly greater than the mean rank ALP for NAF=42.76, P=0.0044 and mean rank of the control group=27.3, p<0.05. Additionally, the mean NAF rankings were significantly higher than those of the control group (P=0.036). The averages and box plot are shown in Figure 2.



Dunn's multiple comparisons test	Mean rank diff.	Adjusted P-Value
AF vs. NAF	21	0.0044
AF vs. Control	37	<0.0001
NAF vs. Control	15	0.0360

Fig 2: Mean ranks values and pairwise comparison of serum ALP in patients and control

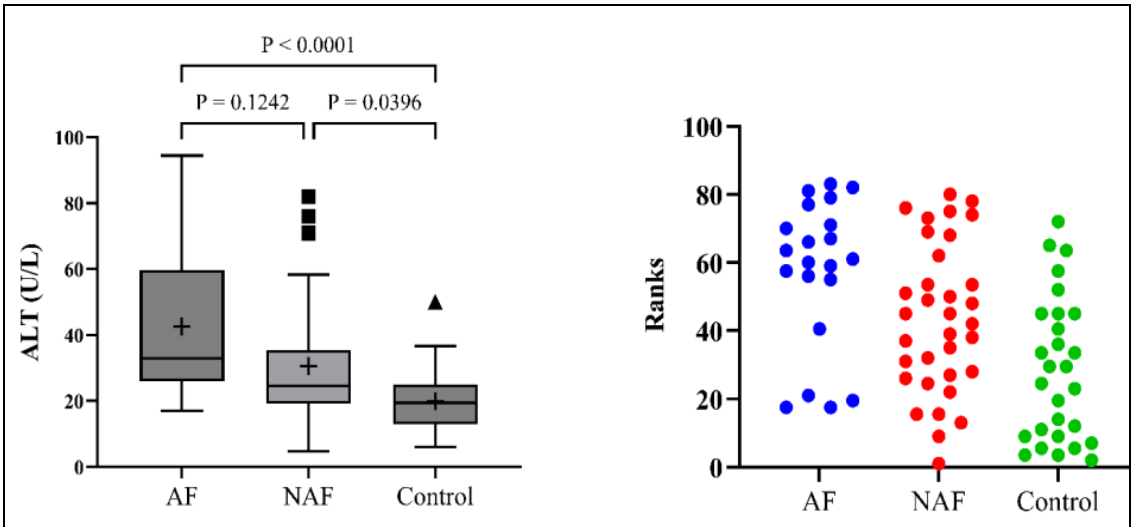
For AF, serum AST had a mean of (53.48±31.56 u/l), (median=40.10 u/l). For NAF, serum AST had a mean of (25.96±9.56 u/l), (median=21.40 u/l). For control, serum AST had a mean of (19.78±5.02 u/l), (median=18.75 u/l). The ranks of the AST among the groups were compared using Kruskal-Wallis the results showed that the mean rank of AST for AF (65.23) was significantly higher than the mean rank AST for NAF (41.19), p<0.0001, and that for control (26.23), p=0 .0004. In addition to these effects, we found statistically significant difference between NAF and control groups P=0.0485. As in Figure 3 display the means and comparisons between the groups.



Dunn's multiple comparisons test	Mean rank diff.	Adjusted P-Value
AF vs. NAF	25	0.0004
AF vs. Control	40	<0.0001
NAF vs. Control	15	0.0485

Fig 3: Mean ranks values and pairwise comparison of serum AST in patients and control

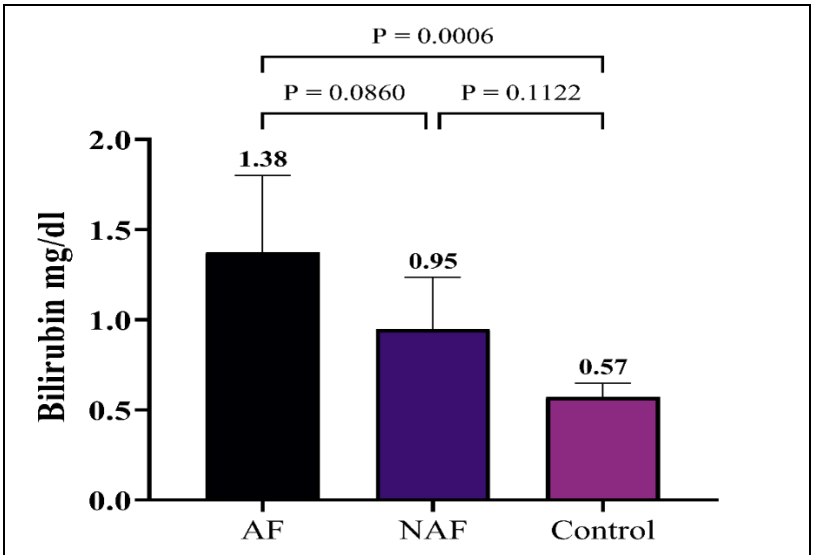
For AF, serum ALT had a mean of (42.58±24.18 u/l), *(median*=34.00 u/l). For NAF, serum ALT had a mean of (30.55±18.64 u/l, *(median*=24.50). For control, serum ALT had a mean of (19.94±9.87) and *median*=(19.50 u/l). The summary statistics can be found in Table (3-6). The results of the Kruskal-Wallis test were significant, *p*<.001, indicating there were significant differences in ranks of serum ALT among the group. Multiple pairwise comparison revealed that the mean rank of ALT for AF (*58.16*) was significantly larger than for control (28.48*), p <0.0001*, and the mean rank of ALT for NAF (43.91) was also significantly higher than that for control P=0.039. No other significant effects were found. Figure 4 display the means and comparisons between the groups.



Dunn's multiple comparisons test	Mean rank diff.	Adjusted P Value
AF vs. NAF	14	0.1242
AF vs. Control	29	<0.0001
NAF vs. Control	15	0.0396

Fig 4: Mean ranks values and pairwise comparison of serum ALT in patients and control

For AF, the mean of bilirubin level was (1.38±0.96 mg/dl). The mean of bilirubin level for NAF was (0.95±0.82 mg/dl). For control, the mean level of bilirubin was (0.57±0.20 mg/dl). Bilirubin was different between the groups, {F (2, 81)=7.55, *p*<.001}. Multiple pairwise comparisons showed that the mean level of bilirubin in AF (M=1.38±SD=0.96 mg/dl) was much higher than in the control group (M=0.57±SD=0.20 mg/dl), with a p-value of less than 0.001. There were no additional significant effects found. Figure 5 show the group means and how they compare to each other.



Turkey's multiple comparisons test	Adjusted P-Value
AF vs. NAF	0.0860
AF vs. Control	0.0006
NAF vs. Control	0.1122

Fig 5: Mean values and 95% CI of the means for bilirubin by groups

The correlation analysis revealed that serum bilirubin demonstrated a significant positive association with reelin (r=0.479), indicating a large effect size (P=0.024). This finding suggests that higher reelin levels are generally associated with increased bilirubin concentrations. No other significant correlations were observed in this group. In the non-advanced fibrosis group, alkaline phosphatase (ALP) showed a strong positive correlation with reelin (r=0.595), also representing a large effect size (P=0.0002). This suggests that ALP levels tend to rise in parallel with increasing reelin concentrations. No other biochemical parameters demonstrated statistically significant correlations with reelin. To further examine whether reelin levels influenced the likelihood of advanced fibrosis (AF) compared with non-advanced fibrosis (NAF), a multinomial logistic regression analysis was performed using an alpha level of 0.05. The overall model was statistically significant, $\chi^2(1)=36.84$, $p<0.001$, indicating that reelin levels significantly affected the odds of being classified in the AF category relative to NAF. Within the AF group, the regression coefficient for reelin was statistically significant (B=0.41, $\chi^2=9.62$, P=0.002). This coefficient translates to an odds ratio (OR) of 1.51 (95% CI: 1.16-1.96), indicating that each one-unit increase in reelin level increases the odds of having advanced fibrosis by approximately 51% compared with non-advanced fibrosis. These findings underscore the potential of reelin as a predictive biomarker for advanced fibrosis in CLD patients, with meaningful correlations to certain liver function parameters, particularly bilirubin in AF and ALP in NAF groups. As in Table 4.

Table 4: Correlation of serum reelin with clinical and biochemical parameters and logistic regression analysis

Group	Variable	N	Correlation Coefficient (r)	P-Value	Interpretation
AF	Bilirubin	22	0.479	0.024	Significant
AF	ALP	22	0.167	0.4577	NS
AF	ALT	22	-0.213	0.3423	NS
AF	AST	22	-0.047	0.8371	NS
AF	BMI	22	-0.291	0.1889	NS
AF	Age	22	-0.009	0.9681	NS
NAF	Bilirubin	34	0.256	0.1439	NS
NAF	ALP	34	0.595	0.0002	Significant
NAF	ALT	34	0.287	0.0996	NS
NAF	AST	34	-0.006	0.9735	NS
NAF	BMI	34	0.063	0.7217	NS
NAF	Age	34	0.137	0.439	NS
Control	Bilirubin	28	-0.145	0.4616	NS
Control	ALP	28	-0.274	0.1581	NS
Control	ALT	28	0.057	0.7745	NS
Control	AST	28	-0.064	0.7447	NS
Control	BMI	28	0.153	0.4356	NS
Control	Age	28	-0.145	0.4621	NS

Logistic Regression Analysis for Predicting Advanced Fibrosis (AF)

Variable	B	SE	χ^2	P-Value	OR	95% CI
Intercept	-2.52	0.61	16.80	<0.001	0.08	[0.02, 0.27]
Reelin	0.41	0.13	9.62	0.002	1.51	[1.16, 1.96]

AF vs. Control: Reelin demonstrated excellent diagnostic accuracy for distinguishing advanced fibrosis (AF) subjects from healthy controls, with an area under the curve (AUC) of 0.945 (95% CI: 0.841-0.990, p<0.001). At an optimal cutoff value of 2.124 ng/mL, the sensitivity was 90.91% and the specificity was 96.43%. NAF vs. Control: Reelin performed poorly in differentiating non-advanced fibrosis (NAF) subjects from healthy controls, yielding an AUC of 0.520 (95% CI: 0.389-0.649, P=0.7912). At a cutoff value of 1.856 ng/mL, the sensitivity was 35.29% and the specificity was 85.71%. AF vs. NAF: Reelin exhibited excellent accuracy in distinguishing AF from NAF, with an AUC of 0.934 (95% CI: 0.835-0.983, p<0.0001). At a cutoff value of 2.403 ng/mL, the sensitivity was 90.91% and the specificity was 88.24%. These findings indicate that serum reelin is a highly effective biomarker for differentiating advanced fibrosis from both healthy controls and non-advanced fibrosis, but has limited value in distinguishing non-advanced fibrosis from healthy individuals, As in Table 5.

Table 5: Area under the ROC curve (AUC) characteristics of reelin as classifying between the study groups

Comparison	Area under the ROC curve	Standard Error	95% Confidence Interval	Significance level (p)	Associated Criterion	Sensitivity (%)	Specificity (%)	+LR	-LR
AF vs Control	0.945	0.0342	0.841 - 0.990	<0.0001	>2.124	90.91	92.86	25.43	0.094
NAF vs Control	0.520	0.0754	0.389 - 0.649	0.7912	>1.833	55.17	52.17	1.24	0.86
AF vs NAF	0.934	0.0325	0.835 - 0.983	<0.0001	>2.674	90.91	86.36	7.34	0.10

Discussion

Non-invasive biomarkers for assessing and monitoring hepatic fibrosis are of considerable clinical interest, particularly for evaluating therapeutic efficacy and prognosis [16]. To our knowledge, this is the first study in Iraq to investigate serum reelin as a potential non-invasive predictor of liver fibrosis in chronic liver disease (CLD) without comparison to liver biopsy or other serological markers such as hyaluronic acid or alpha-fetoprotein. Previous studies have shown that the liver, particularly hepatic stellate cells (HSCs), is the primary source of circulating reelin [17, 18], in addition to its established role in neuronal development [17]. In this study, after applying strict exclusion criteria and discarding hemolyzed samples (per manufacturer instructions), three groups remained: 28 apparently healthy controls, 34 patients with non-advanced fibrosis (NAF; F0-F2), and 22 with advanced fibrosis (AF; F3/F4). Age was not significantly different among groups, minimizing confounding due to biological variation. Serum reelin levels were significantly higher in AF compared to both NAF and controls (p≤0.05), while no significant difference was observed between NAF and controls (P=0.9653). These findings suggest that reelin elevation is more prominent in advanced fibrosis, likely due to cross-talk between ductular reaction (DR) cells and activated reelin-positive HSCs/myofibroblasts [19]. DR cells expressing Dab1 may facilitate reelin-mediated signaling in hepatic progenitor cells, contributing to fibrogenesis.

Our results align with Mansy et al. [20], who demonstrated significantly elevated reelin in advanced fibrosis, with good diagnostic accuracy for F2-F4 stages (AUC 0.859-0.871). This agreement may reflect similar sample sizes, narrower etiological inclusion criteria, and the use of ELISA for reelin measurement. In contrast, Sturm et al. [21] reported no significant differences in reelin levels across fibrosis stages (P=0.12-0.18) and only modest correlation with fibrosis (AUC=0.79). This discrepancy may relate to their inclusion of heterogeneous CLD etiologies, hepatocellular carcinoma, and broader demographic variation. In our cohort, serum reelin correlated weakly with liver function parameters, except for bilirubin in AF (P=0.024) and ALP in NAF (P=0.0002). This is consistent with Sturm et al. [21], who also found weak correlations with AST and ALT, though their bilirubin association differed, possibly due to differences in exclusion criteria, comorbidities, and population characteristics. The observed associations may indicate that reelin expression increases with fibrosis progression and declining hepatic function. Limitations include the absence of liver biopsy confirmation, although transient elastography has been validated in multiple biopsy-controlled studies for high sensitivity and specificity in diagnosing fibrosis and cirrhosis [22, 23]. Nonetheless, the present findings support serum reelin as a promising non-invasive marker for advanced hepatic fibrosis, warranting further validation in larger, etiologically diverse cohorts.

Conclusion

Blood reelin may have excellent diagnostic utility in the differentiation of advanced hepatic fibrosis from healthy subjects and those with non-advanced hepatic fibrosis. Blood reelin, on the other hand, had poor diagnostic utility in the diagram of each stage of non-advanced hepatic fibrosis due to the small fibrosis size.

Conflict of Interest

Not available

Financial Support

Not available

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How to Cite This Article
Al-Saffar RM, Al-Wasiti E, Askaar B. Evaluation of relation of serum reelin and stages of liver fibrosis in a sample of Iraqi patients with chronic liver disease. International Journal of Clinical and Diagnostic Pathology. 2025;8(3):49-57.