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The Relationship Between The Expression Of LRP1, LDLR, And LOX1 Receptors With The Steatosis Index And Liver Stiffness In Patients With Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a multifactorial condition characterized by complex interactions between metabolic dysfunction, lipid accumulation, inflammation, and progressive fibrosis. Molecular mechanisms underlying these processes increasingly highlight the role of receptor genes involved in lipid transport and oxidative stress regulation. The present study aimed to investigate the association between the expression levels of LRP1, LDLR, and LOX1 receptor genes and key morphometric and non-invasive indicators of hepatic involvement in NAFLD. A cohort of patients with varying degrees of steatosis and fibrosis underwent molecular-genetic analysis, elastographic assessment of liver stiffness (Young's modulus), and evaluation of the Fatty Liver Index (FLI).

The results demonstrated that decreased expression of LRP1 and LDLR was significantly associated with higher FLI values, indicating a potential contribution of impaired receptor-mediated lipid uptake to the amplification of hepatic steatosis. These findings may reflect reduced hepatic clearance of circulating lipoproteins and altered lipid handling within hepatocytes, promoting intracellular lipid overload. In contrast, LOX1 expression showed a weak but statistically significant positive correlation with liver stiffness measurements, suggesting that oxidative stress and oxLDL-mediated signaling may participate in the early development of fibrosis. LOX1-dependent pathways are known to activate pro-inflammatory cascades, endothelial dysfunction, and extracellular matrix remodeling—mechanisms that could influence fibrogenesis in NAFLD.

Collectively, the obtained data indicate that alterations in the expression profiles of LRP1, LDLR, and LOX1 may serve as molecular indicators of steatosis severity and early fibrotic changes. These genes may represent promising biomarkers for identifying patients at risk of progressive liver injury and developing personalized therapeutic strategies aimed at modifying lipid metabolism and oxidative stress. Further studies with larger cohorts and longitudinal follow-up are required to clarify the causal relationships and determine their potential as predictive markers in clinical practice.

Keywords: - Non-alcoholic fatty liver disease (NAFLD); gene expression; LRP1; LDLR; LOX1; liver steatosis; Young's modulus; liver stiffness; Fatty Liver Index (FLI); oxidative stress; lipid metabolism; hepatic fibrosis; molecular biomarkers; metabolic dysfunction.

INTRODUCTION

In recent years, increasing attention has been paid to studying the molecular mechanisms underlying metabolic liver diseases. One such condition is non-alcoholic fatty liver disease (NAFLD), the prevalence of which is steadily rising worldwide and reaches 25–30% in the general adult population [5]. NAFLD is associated not only with insulin resistance and metabolic syndrome but also with the risk of progression to liver fibrosis and cirrhosis [3]. The receptors LRP1, LDLR, and LOX1 are involved in inflammation processes, lipid transport, and the development of metabolic disturbances [1, 2]. Therefore, investigating the relationship between the expression levels of these receptor genes and the morphological characteristics of the liver is both relevant and promising for stratifying patients with NAFLD.

METHODS

The study included patients with a confirmed diagnosis of non-alcoholic fatty liver disease (NAFLD) who underwent evaluation of the liver fat infiltration index (Fatty Liver Index – FLI) and liver stiffness, determined by the median of Young's modulus using elastography. Concurrently, the levels of LRP1, LDLR, and LOX1 gene expression were assessed by quantitative polymerase chain reaction (qPCR). Correlation analysis was performed using Pearson's correlation coefficient. Statistical significance was set at $p<0.05$.

DISCUSSION OF RESULTS

The correlation between the median of the liver's Young's modulus (in kPa) — a parameter that characterizes the elasticity (stiffness) of liver tissue — and the expression level of LRP1 was examined. According to the results of the correlation analysis, the Pearson correlation coefficient was $r = -0.02$, indicating an almost complete absence of a linear relationship between the studied variables (Figure 1).

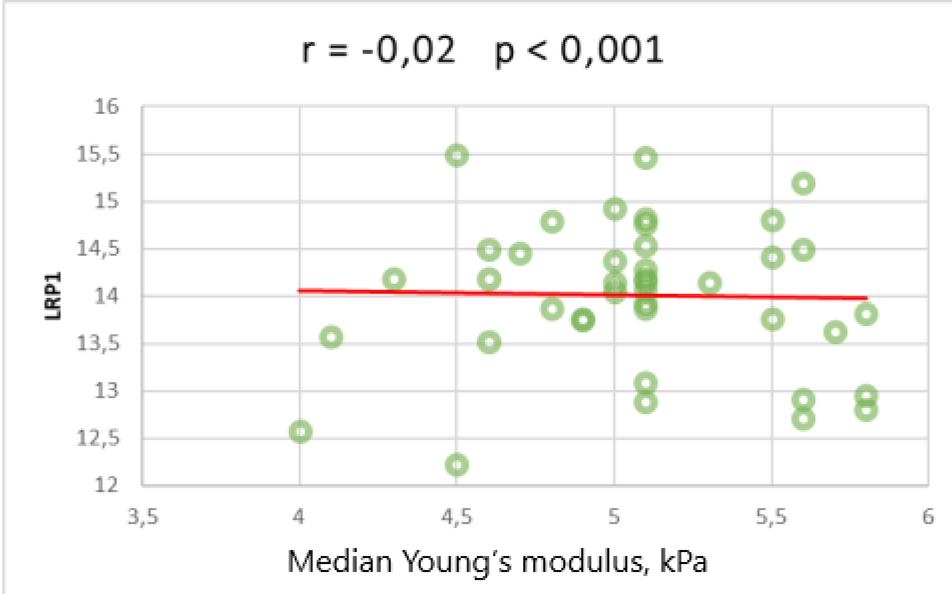

Figure 1. Correlation between the median of Young's modulus (in kPa) and the level of LRP1 gene expression.

The level of statistical significance was p<0.001, which formally indicates the statistical significance of the detected (though extremely weak) relationship. From a practical perspective, such a low correlation coefficient suggests that changes in liver stiffness do not have a significant impact on LRP1 receptor expression, and, therefore, there is most likely no biologically significant relationship between these parameters.

LDLR is a multifunctional receptor involved in the regulation of lipid metabolism, inflammation, and cell migration. The Young's modulus of the liver reflects fibrotic changes and the organ's elasticity. Figure 2 shows the correlation between these variables.

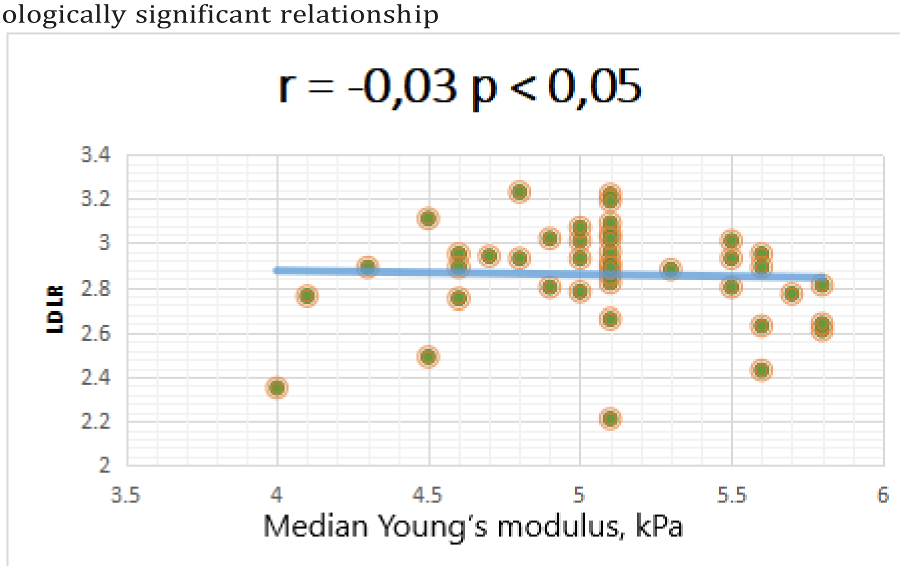

Figure 2. Correlation between the median of the Young's modulus (in kPa) and the expression level of LDLR

This figure demonstrates the almost complete absence of a linear relationship between the median of the Young's modulus and the expression level of LDLR. It is possible that the expression of the receptor gene is regulated by other factors such as metabolic status, lipid profile, insulin resistance, or inflammation, which are not directly associated with changes in the liver tissue stiffness, measured through elastography.

Figure 3. Correlation between the median of the Young's modulus (in kPa) and the expression level of LOX1 protein

This figure shows a weak positive correlation with high statistical significance ($p < 0.001$).

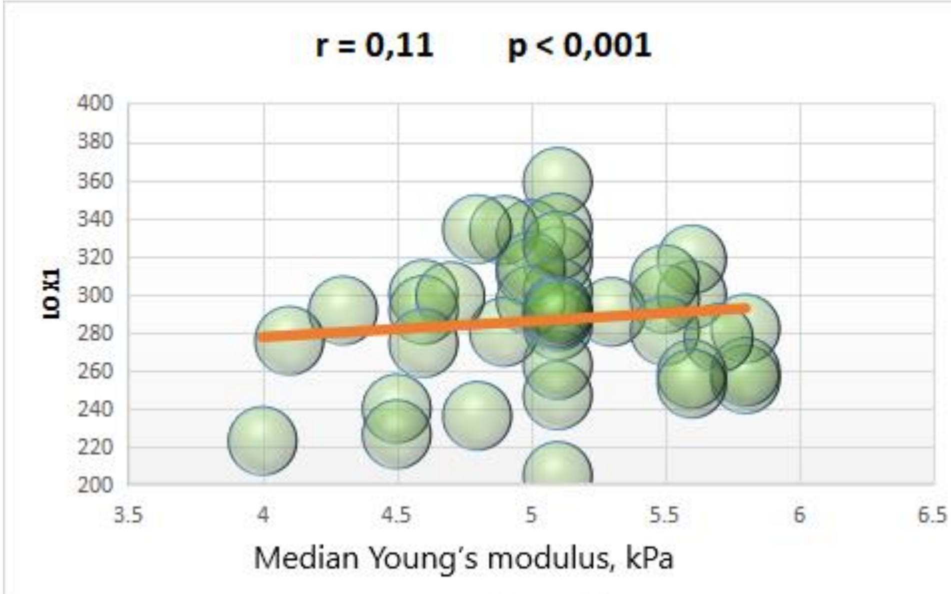

Figure 3. Correlation between the median of the Young's modulus (in kPa) and the expression level of LOX1 protein

Although the strength of the correlation is minimal, the statistically significant p-value suggests a weak but consistent trend towards increased expression of LOX1 with rising liver stiffness values.

The obtained data demonstrate that the expression of LRP1 and LDLR receptors decreases as the degree of liver fat infiltration increases, which aligns with previously published studies [1, 2, 5, 8, 9]. These receptors play an important role in the removal of lipoproteins and protection against inflammatory reactions. On the other hand, LOX1 expression showed a weak positive correlation with liver stiffness values, which could be associated with enhanced oxidative stress and the activation of fibrosis. Similar changes have been previously described in other studies [3, 4, 6, 7]. However, the weak correlation strength suggests that the expression of these receptors may be regulated by a broader range of factors, including inflammation, insulin resistance, and metabolic background.

Additionally, we studied the correlation between the fatty liver index (FLI, on the X-axis) and the expression level of the lipoprotein receptor associated with receptor 1 (LRP1, on the Y-axis) (Figure 4).

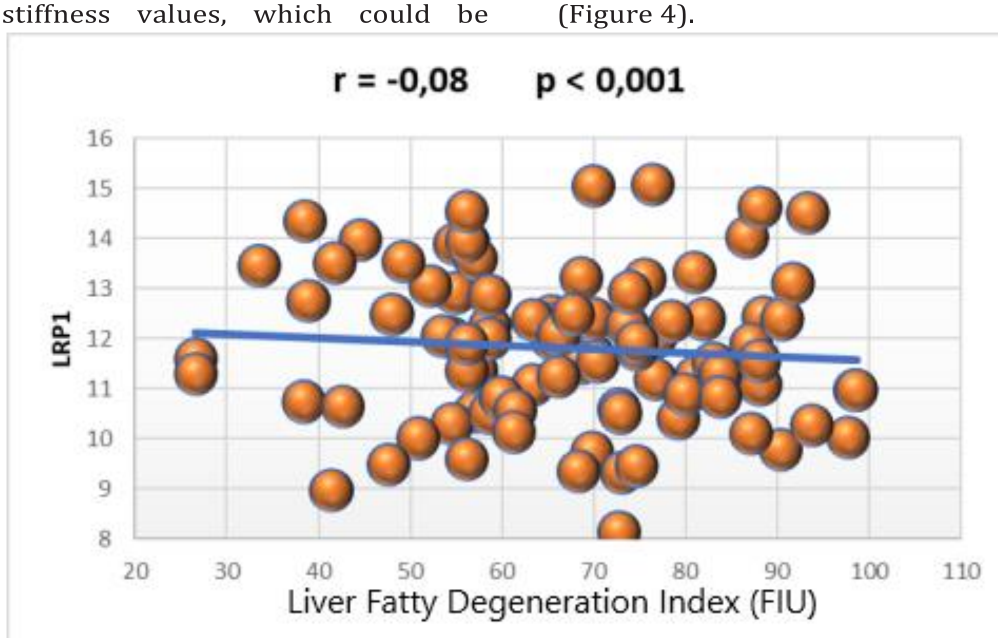

Figure 4. Correlation between the fatty liver index (FLI) and the level of LRP1 expression.

The analysis revealed a very weak negative correlation between these indicators (r = –0.08), while the relationship was statistically significant (p < 0.001). The decrease in LRP1 levels with increasing FLI indicates a possible trend toward impaired lipid transport and metabolism in more pronounced hepatic steatosis. However, given the extremely low correlation coefficient, it can be concluded that this relationship is minimally expressed. Nonetheless, the statistical significance suggests the presence of a non-random trend that requires further clarification in multifactorial models. Functionally, LRP1 is involved in lipoprotein clearance and the regulation of inflammatory reactions, which could be associated with the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Thus, even a slight decrease in its level may reflect early metabolic disturbances in the context of steatosis.

The relationship between LRP1 expression and FLI showed negative, statistically significant correlations, indicating a reduction in receptor activity mechanisms as hepatic steatosis progressed. However, the degree of correlation remained weak, underscoring the limited predictive power of this indicator.

The correlations with the Young's modulus were extremely weak, and in some cases, did not reach statistical significance, which prevents these markers from being considered reliable indicators of the degree of fibrotic changes.

Thus, the identified relationships confirm the involvement of the LRP1, LDLR, and LOX1 receptors in the pathogenesis of cardiometabolic disorders in NAFLD, but the absence of strong linear connections points to the multifactorial nature of the pathological process. The obtained results highlight the need for further research with expanded sample sizes and the inclusion of additional pathophysiological variables to clarify the role of these molecular markers in clinical risk stratification.

This suggests that as the degree of liver steatosis increases (indicated by a higher FLI), the expression level of LRP1 decreases, which may reflect lipid and lipoprotein metabolism disturbances associated with the progression of hepatic fat infiltration. As known, LRP1 is a receptor that plays an important role in the clearance of lipoproteins, regulation of inflammation, and transport of cholesterol and other molecules. The decrease in LRP1 expression may contribute to the accumulation of atherogenic lipids and worsen metabolic disturbances. Liver steatosis is associated with insulin resistance, hyperlipidemia, and systemic inflammation—all of which may potentially inhibit LRP1 expression, as confirmed by the observed inverse correlation in the figure. The moderate, statistically significant negative correlation between FLI and LRP1 expression may indicate the involvement of LRP1 in the pathogenesis of NAFLD and its progression, accompanied by lipid metabolism disturbances, as well as reduced receptor activity. These data require further investigation to evaluate LRP1 as a potential biomarker of metabolic and hepatogenic disturbances.

Figure 7 presents the correlation between FLI and the expression level of LDLR.

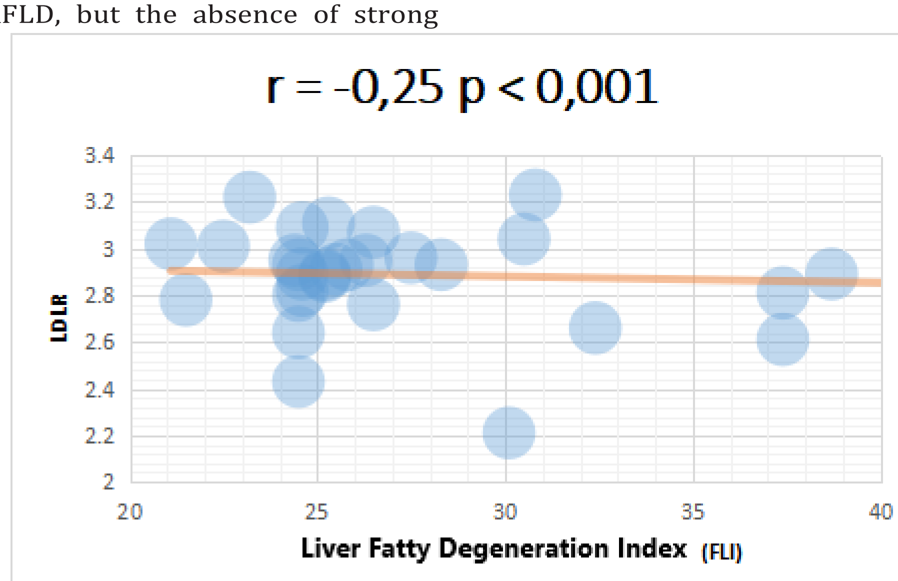

Figure 7. Correlation between the fatty liver index (FLI) and the expression level of LDLR protein.

The Pearson correlation coefficient was r = −0.25, indicating a weak negative correlation between the two indicators with high statistical significance ($p < 0.001$). Although the strength of the correlation is low, the significance of the result suggests a trend toward a decrease in LDLR levels as the severity of liver fat infiltration (increase in FLI) progresses. This may reflect metabolic disturbances associated with the progression of NAFLD.

The Young's modulus, which reflects liver stiffness, showed extremely weak or no correlations with gene expression, indicating the complex nature of the relationships between liver morphological changes and molecular markers.

The correlation between FLI and the expression of LRP1 and LDLR was negative. This indicates that as steatosis increases, there is a decrease in the expression of lipid metabolism receptors, confirming the role of these molecules in the development of metabolic disturbances.

DISCUSSION

The findings of this study provide new insight into the molecular mechanisms underlying hepatic steatosis and early fibrotic changes in patients with non-alcoholic fatty liver disease (NAFLD). By analyzing the expression levels of the receptor genes LRP1, LDLR, and LOX1 in relation to the Fatty Liver Index (FLI) and liver stiffness (Young's modulus), the study highlights the complex and multifactorial nature of molecular disturbances associated with NAFLD. Although the identified correlations were generally weak, their consistency and statistical significance suggest that changes in receptor expression reflect biologically relevant processes related to lipid metabolism, oxidative stress, and hepatic remodeling.

The decrease in LRP1 expression with rising FLI aligns with the known functional role of LRP1 in regulating lipid transport, inflammatory responses, and hepatic lipid clearance. LRP1 participates in the uptake of triglyceride-rich lipoproteins and is essential for maintaining intracellular lipid homeostasis. Reduced expression of LRP1 may result in impaired lipid clearance, contributing to hepatic triglyceride accumulation and steatosis. This relationship, although weak, is biologically plausible and consistent with the "multiple-hit" model of NAFLD pathogenesis, which posits that impaired lipid handling and systemic metabolic disturbances jointly accelerate steatotic progression. A decline in LRP1 expression may therefore represent an early molecular marker of lipid overload, preceding more pronounced inflammatory or fibrotic changes.

Similarly, LDLR expression demonstrated a weak but significant negative correlation with FLI, indicating that worsening steatosis is associated with reduced LDLR-mediated lipoprotein uptake. LDLR is the primary receptor responsible for clearing circulating LDL cholesterol, and its downregulation can contribute to hyperlipidemia, oxidative stress, and hepatic lipotoxicity. The observed relationship suggests that as steatosis intensifies, LDLR expression becomes progressively disrupted, further exacerbating metabolic imbalance. Although the correlation coefficient remained low, the pattern is consistent with previous research indicating that diminished LDLR activity contributes to both hepatic fat accumulation and systemic atherogenic risk. From a mechanistic standpoint, reduced LDLR expression may also be linked to insulin resistance and inflammatory signaling, both of which are key drivers of NAFLD progression.

In contrast to LRP1 and LDLR, the expression of LOX1 demonstrated a weak positive correlation with liver stiffness. LOX1, a receptor responsible for binding oxidized LDL (oxLDL), plays a central role in oxidative stress–mediated damage, endothelial dysfunction, and activation of fibrogenic pathways. The observed trend toward increased LOX1 expression in patients with higher Young's modulus may reflect early fibrotic processes associated with chronic inflammation and oxidative injury. While the magnitude of the correlation was small, the direction of the association is consistent with known LOX1 mechanisms: activation of NF-κB, stimulation of inflammatory cytokines, promotion of extracellular matrix deposition, and induction of hepatocellular stress responses. These processes collectively contribute to structural liver changes that may eventually manifest as clinically significant fibrosis.

Despite these mechanistic compatibilities, the generally weak correlations emphasize that gene expression alone cannot fully capture the multifactorial complexity of NAFLD. Liver stiffness does not solely depend on receptor-mediated molecular mechanisms; it reflects a composite of inflammation, extracellular matrix deposition, metabolic stress, insulin resistance, and hepatocellular injury. Therefore, the absence of strong correlations with Young's modulus is not unexpected. Similarly, steatosis severity—

measured by FLI—represents a multifaceted metabolic process influenced by adipose tissue dysfunction, dietary factors, genetic predispositions, and hormonal influences, which collectively extend beyond the regulatory scope of individual receptor genes.

The findings also highlight the distinction between steatosis and fibrosis as overlapping but biologically divergent processes. While LRP1 and LDLR expression was more closely related to steatosis, LOX1 expression showed tendencies associated with early fibrosis. These patterns are consistent with the sequence of molecular events described in contemporary NAFLD models, where lipid accumulation precedes oxidative stress, inflammation, and fibrotic remodeling. LOX1-related pathways may become progressively more dominant as the disease transitions from steatosis to steatohepatitis and early fibrosis. Thus, the observed associations may reflect the temporal dynamics of receptor expression during NAFLD progression.

The statistically significant yet weak correlations across all receptors underscore that NAFLD pathogenesis is shaped by a broad network of interacting factors. These include mitochondrial dysfunction, adipokine imbalance, gut microbiota alterations, epigenetic regulation, and systemic inflammatory mediators. Gene expression changes in LRP1, LDLR, and LOX1 likely represent only one component of a much larger pathophysiological system. This complexity also highlights the challenges of identifying single molecular markers that reliably predict hepatic remodeling, and supports the need for multivariate analytic approaches incorporating genetic, metabolic, inflammatory, and imaging parameters.

Additionally, the findings suggest potential clinical relevance. Even weak but consistent alterations in receptor expression may serve as early indicators of metabolic dysregulation in NAFLD patients. LRP1 and LDLR expression changes, associated with higher steatosis, may help identify patients at risk for more rapid metabolic deterioration. LOX1 expression, associated with increased liver stiffness, may provide insight into oxidative stress–driven fibrogenic activity. While these markers are not sufficiently robust to serve as standalone diagnostic tools, they may contribute to composite biomarker panels that improve risk stratification and monitoring in NAFLD.

However, the results must be interpreted with caution. The weak correlations highlight the need for larger cohort studies, longitudinal designs, and evaluation of additional variables such as inflammatory cytokines, lipid subfractions, mitochondrial markers, and epigenetic regulators. Moreover, the cross-sectional nature of the current study limits causal inference, and gene expression patterns may vary depending on disease stage, metabolic background, and individual genetic susceptibility.

In conclusion, the study demonstrates that decreased expression of LRP1 and LDLR is associated with a higher degree of hepatic steatosis, while LOX1 expression shows a weak tendency to increase with liver stiffness. These findings support the involvement of receptor-mediated lipid and oxidative pathways in the pathogenesis of NAFLD but also reveal the multifactorial nature of hepatic remodeling. The limited strength of the correlations emphasizes the need for expanded, multifactorial research to clarify the role of these receptors as potential biomarkers or therapeutic targets in the management of NAFLD.

CONCLUSION

The decrease in the expression of LRP1 and LDLR as FLI increases confirms their involvement in the pathogenesis of hepatic steatosis. LOX1 demonstrates a tendency to increase with the growing stiffness of liver tissue, which may reflect a compensatory response during the progression of fibrosis. However, the weak degree of the identified correlations emphasizes the need for further research using multifactorial models and expanding the patient sample.

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