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Correlation Between Liver Fibrosis Scores (FIB-4, APRI) and Oxidative Stress Biomarkers in Chronic Hepatitis B and C Patients

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ABSTRACT

Background: Chronic hepatitis B (HBV) and hepatitis C (HCV) infections are major causes of progressive liver fibrosis and cirrhosis. Non-invasive fibrosis indices like Fibrosis-4 (FIB-4) and Aspartate Aminotransferase to Platelet Ratio Index (APRI) are commonly utilized in clinical evaluation. Oxidative stress has been identified in liver damage, but its connection with the fibrosis scores needs additional assessment.

Objective: To determine the correlation between liver fibrosis scores (FIB-4, APRI) and oxidative stress biomarkers in patients with chronic hepatitis B and C.

Methods: This cross-sectional study was conducted in the Department of Medicine, Bahawalpur Medical and Dental College, Bahawalpur, Pakistan, over a one-year duration from January 2024 to January 2025. The research included 130 individuals diagnosed with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections. Liver fibrosis was assessed by recognised non-invasive scoring methodologies. Serum oxidative stress indicators, namely malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH), were measured using enzyme-linked immunosorbent assay (ELISA). Data analysis used SPSS version 26, using Pearson correlation and multivariable regression analysis to investigate connections and discern independent relationships among research variables.

Results: The mean FIB-4 and APRI scores were 1.89 ± 0.88 and 1.05 ± 0.52, respectively. MDA levels showed a strong positive correlation with FIB-4 ($r = 0.64$) and APRI ($r = 0.59$) ($p < 0.001$). SOD and GSH demonstrated significant negative correlations with fibrosis scores ($p < 0.01$). Patients with advanced fibrosis exhibited significantly higher MDA and lower antioxidant levels. Multivariate analysis identified MDA as an independent predictor of fibrosis severity ($\beta = 0.53$, $p < 0.001$).

Conclusion: Oxidative stress is strongly associated with liver fibrosis severity in chronic hepatitis patients. Integration of oxidative biomarkers with non-invasive fibrosis scores may improve disease assessment.

Keywords: Chronic hepatitis B, chronic hepatitis C, liver fibrosis, FIB-4, APRI, oxidative stress, malondialdehyde, superoxide dismutase, glutathione

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INTRODUCTION

Chronic hepatitis B (HBV) and hepatitis C (HCV) infections remain major global health concerns, particularly in developing countries such as Pakistan, where the burden of viral hepatitis continues to rise [1]. These infections are important causes of chronic hepatitis and are strongly associated with progressive liver fibrosis, cirrhosis, and hepatocellular carcinoma. The pathogenesis of liver fibrosis involves a complex interplay of persistent viral replication, immune-mediated inflammation, and activation of hepatic stellate cells, ultimately leading to excessive extracellular matrix deposition and distortion of the normal hepatic architecture [2].

Accurate assessment of liver fibrosis is essential for clinical decision-making, including treatment initiation,

monitoring disease progression, and preventing adverse outcomes [3]. Although liver biopsy has traditionally been regarded as the gold standard for fibrosis assessment, its invasive nature, associated risks, sampling variability, and limited patient acceptability have led to the development of non-invasive alternatives. Among these, the Fibrosis-4 (FIB-4) index and the Aspartate Aminotransferase to Platelet Ratio Index (APRI) are widely used due to their simplicity, cost-effectiveness, and reliance on routinely available laboratory parameters. These scoring systems have demonstrated reasonable accuracy in identifying advanced fibrosis and cirrhosis in patients with chronic viral hepatitis [4,5].

In recent years, increasing attention has been directed toward the role of oxidative stress in the pathogenesis of chronic liver diseases [6]. Oxidative stress refers to an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms. Persistent inflammatory activity in chronic HBV and HCV infections promotes excessive ROS generation, resulting in lipid peroxidation, protein oxidation, and DNA damage. This oxidative imbalance not only worsens hepatocellular injury but also contributes to fibrogenesis by activating hepatic stellate cells and increasing the expression of profibrotic cytokines [7].

Biochemical markers of oxidative stress have emerged as potential indicators of disease severity. Malondialdehyde (MDA) is a well-established marker of lipid peroxidation and reflects the extent of oxidative damage in hepatocytes. In contrast, antioxidant enzymes such as superoxide dismutase (SOD) and intracellular antioxidants such as glutathione (GSH) play essential roles in protecting the liver against oxidative injury. Alterations in these biomarkers have been reported in patients with chronic liver disease; however, their direct relationship with established non-invasive fibrosis scores has not been sufficiently explored [8,9].

Evaluating the association between fibrosis indices (FIB-4 and APRI) and oxidative stress biomarkers may provide valuable insights into disease pathophysiology and improve non-invasive assessment strategies. Such an integrated approach may enhance early fibrosis detection, improve risk stratification, and potentially support the development of targeted therapeutic interventions aimed at reducing oxidative damage [10].

The present study aimed to compare liver fibrosis scores (FIB-4 and APRI) with oxidative stress biomarkers (MDA, SOD, and GSH) in patients with chronic hepatitis B and C in order to develop a more robust and clinically applicable model for assessing disease severity [11].

MATERIALS AND METHODS

This cross-sectional research was performed in the Department of Medicine, Bahawalpur Medical and Dental College, Bahawalpur, Pakistan, over a one-year duration from January 2024 to January 2025. The research sought to assess the correlation between liver fibrosis scores and oxidative stress-related indicators in individuals with chronic viral hepatitis. A total of 130 patients were recruited via a non-probability sequential sampling method. The research cohort consisted of persons aged 18 to 65 years who tested positive for serological indicators of chronic hepatitis B (HBsAg) or chronic hepatitis C (anti-HCV antibodies). Inclusion was restricted to patients who furnished written informed permission.

Patients with a history of alcoholic liver disease, co-infection with HIV or other hepatitis viruses, hepatocellular carcinoma, chronic kidney disease, autoimmune liver disease, or current use of antioxidant supplements were excluded to minimize potential confounding factors affecting oxidative stress markers. Following enrollment, detailed demographic and clinical data, including age, sex, duration of illness, and relevant medical history, were recorded using a structured proforma. Approximately 5 mL of venous blood was collected aseptically from each participant for laboratory analysis.

Assessment of hepatic fibrosis was carried out using two validated non-invasive biochemical scoring models derived from routinely available laboratory variables. The Fibrosis-4 Index (FIB-4) was determined using the patient's age, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count. In parallel, the Aspartate Aminotransferase to Platelet Ratio Index (APRI) was calculated by relating AST values to the upper reference limit and platelet count. Elevated values of both scoring systems were considered suggestive of a greater degree of underlying hepatic fibrotic change.

To examine oxidative stress status, serum concentrations of malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH) were analyzed using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Among these markers, MDA was used as an indicator of lipid peroxidation and oxidative cellular injury, whereas SOD and GSH were evaluated as representative components of the body's antioxidant defense system, reflecting enzymatic and non-enzymatic protective mechanisms, respectively. All laboratory estimations were performed under standardized analytical conditions in accordance with the instructions supplied by the kit manufacturers to ensure consistency and reproducibility of results.

The statistical analysis of the research data was performed using SPSS version 26.0. Quantitative data were expressed as mean ± standard deviation, whilst qualitative variables were characterised by frequencies and percentages. The independent samples t-test was used to analyse the differences between study groups. Pearson correlation analysis was used to ascertain the association between liver fibrosis indices (FIB-4 and APRI) and oxidative stress indicators (MDA, SOD, and GSH). Furthermore, multivariable linear regression analysis was used to ascertain characteristics independently correlated

with the severity of liver fibrosis. A p-value below 0.05 was deemed statistically significant.

Ethical permission for this investigation was obtained by the Institutional Review Board of Bahawalpur Medical College, Bahawalpur, Pakistan, under Reference No. IRB/BMDC/2024/041. The research was executed in compliance with established ethical standards for human studies. Before recruitment, signed informed permission was obtained from all participants, and the confidentiality of the gathered data was preserved throughout the research duration.

RESULTS

A total of 130 patients with chronic viral hepatitis were included in the analysis, comprising 62 (47.7%) patients with hepatitis B and 68 (52.3%) with hepatitis C. The mean age of the participants was 43.7 ± 11.3 years, with a predominance of males (61.5%) compared to females (38.5%). Most participants were middle-aged, reflecting the typical demographic distribution of chronic liver disease. Initial biochemical analysis revealed high liver enzyme levels that were in line with the presence of hepatic inflammation. The study population was well balanced in the presence of both HBV and HCV as indicated in Table 1 with moderately elevated liver enzymes that depict active disease.

The mean Fibrosis-4 (FIB-4) score was 1.89 ± 0.88, while the mean Aspartate Aminotransferase to Platelet Ratio Index (APRI) was 1.05 ± 0.52, suggesting a broad spectrum of fibrosis severity among the participants. Oxidative stress was assessed, and the levels of malondialdehyde (MDA) were found to be significantly higher, with lower levels of antioxidant markers, such as superoxide dismutase (SOD) and glutathione (GSH). These findings indicate a pronounced oxidative stress state in patients with chronic hepatitis. Higher levels of MDA and lower levels of SOD and GSH indicate an increase in oxidative damage and a reduction in antioxidant defense mechanisms (Table 2).

Pearson correlation analysis demonstrated a statistically significant association between liver fibrosis scores and oxidative stress biomarkers. MDA showed a strong positive correlation with both FIB-4 and APRI scores, whereas antioxidant markers exhibited an inverse relationship. As detailed in Table 3, MDA demonstrated a strong positive correlation with FIB-4 ($r = 0.64$) and APRI ($r = 0.59$), both highly significant ($p < 0.001$), indicating that increased lipid peroxidation is associated with fibrosis progression. Contrary to this, SOD and GSH exhibited moderate, albeit statistically significant, negative correlations, indicating that loss of antioxidant defense is matched by a rise in the severity of fibrosis.

Patients were further stratified into low and high fibrosis groups based on FIB-4 cut-off values. Significant differences were observed between these groups in terms of oxidative stress and antioxidant levels. As shown in Table 4, patients with advanced fibrosis exhibited significantly higher MDA levels and significantly lower SOD and GSH levels compared to those with mild fibrosis, reinforcing the association between oxidative stress and fibrosis severity.

The multivariate linear regression analysis was conducted to determine independent predictors of liver fibrosis, using FIB-4 score as a dependent variable. The model incorporated both oxidative stress biomarkers and applicable clinical variables. As presented in Table 5, MDA emerged as a strong independent predictor of fibrosis severity ($\beta = 0.53$, $p<0.001$). Fibrosis was also significantly related to age and AST levels, which align with their known roles in disease progression. In contrast, SOD and GSH did not retain statistical significance after adjustment, suggesting that while antioxidant depletion is associated with fibrosis, oxidative damage as reflected by MDA has a more prominent independent effect.

Overall, the findings demonstrate a consistent and statistically significant association between oxidative stress and the severity of liver fibrosis, highlighting the potential value of integrating oxidative biomarkers with non-invasive fibrosis indices to enhance clinical assessment.

Table 1: Baseline Characteristics of Study Participants (n = 130)

Variable	Value
Age (years)	43.7 ± 11.3
Male (%)	80 (61.5%)
Female (%)	50 (38.5%)
HBV patients	62 (47.7%)
HCV patients	68 (52.3%)
ALT (IU/L)	58.9 ± 19.6
AST (IU/L)	54.3 ± 18.2
Platelet count (×10⁹/L)	182 ± 54

Table 2: Fibrosis Scores and Oxidative Stress Biomarkers

Parameter	Mean ± SD
FIB-4 score	1.89 ± 0.88
APRI score	1.05 ± 0.52
MDA (nmol/mL)	4.6 ± 1.5
SOD (U/mL)	2.4 ± 0.8
GSH (µmol/L)	5.3 ± 1.6

Table 3: Correlation of Fibrosis Scores with Oxidative Stress Biomarkers

Parameter	FIB-4 (r)	APRI (r)	p-value
MDA	+0.64	+0.59	<0.001
SOD	-0.48	-0.45	<0.01
GSH	-0.52	-0.49	<0.01

Table 4: Comparison of Oxidative Stress Markers by Fibrosis Severity

Parameter	Low Fibrosis	High Fibrosis	p-value
MDA (nmol/mL)	3.8 ± 1.2	5.7 ± 1.4	<0.001
SOD (U/mL)	2.8 ± 0.7	2.0 ± 0.6	0.002
GSH (µmol/L)	6.1 ± 1.4	4.5 ± 1.2	<0.001

Table 5: Multivariate Linear Regression Analysis for Predictors of Liver Fibrosis (FIB-4 as Dependent Variable)

Variable	β Coefficient	Standard Error	t-value	p-value
MDA	0.53	0.08	6.62	<0.001
SOD	-0.12	0.07	-1.71	0.089
GSH	-0.15	0.09	-1.88	0.063
Age	0.21	0.06	3.50	0.001
AST	0.18	0.07	2.57	0.012

DISCUSSION

The present study compared non-invasive liver fibrosis scores (FIB-4 and APRI) with oxidative stress biomarkers in patients with chronic hepatitis B and C and found a strong and statistically significant correlation between oxidative stress and the severity of fibrosis [1]. The findings indicate that higher fibrosis scores are associated with greater oxidative injury, particularly reflected by elevated malondialdehyde (MDA) concentrations, along with depletion of antioxidant defenses, including superoxide dismutase (SOD) and glutathione (GSH) [2].

The FIB-4 and APRI scores in the present study showed a wide distribution among the participants, indicating varying degrees of fibrosis severity within the study population. These non-invasive and well-validated tools are considered reliable for the assessment of liver fibrosis, particularly in resource-limited settings where liver biopsy may not be feasible [3]. The observed increase in fibrosis scores, especially among patients with hepatitis C, is consistent with the more aggressive fibrogenic potential of HCV infection compared with HBV, likely due to persistent immune activation and associated metabolic alterations [4].

One of the most important findings of this study was the strong positive correlation between MDA levels and liver fibrosis scores (FIB-4 and APRI) [5]. MDA, an end product of lipid peroxidation, serves as a direct marker of oxidative damage to hepatocyte membranes. The significantly elevated MDA levels observed in patients with higher fibrosis scores suggest that oxidative stress is not merely a consequence of liver injury but may also actively contribute to fibrosis progression. Chronic viral infections are known to induce sustained generation of reactive oxygen species (ROS), which activate hepatic stellate cells and promote collagen deposition and fibrotic remodeling of liver tissue [6-8].

Conversely, the research also revealed significant negative correlations between antioxidant biomarkers (SOD and GSH) and fibrosis scores [9]. This indicates that the endogenous antioxidant defense mechanisms are gradually exhausted with the worsening of liver diseases. SOD is important in the disproportion of the superoxide radicals and GSH is vital in the detoxification of the reactive intermediates and preservation of the redox balance. Their reduced levels in patients with advanced fibrosis indicate an overwhelmed antioxidant defense system that is no longer capable of effectively counteracting excessive oxidative stress [10].

Multivariate regression analysis further supported these observations by identifying MDA as an independent predictor of liver fibrosis, even after adjustment for confounding variables. This finding suggests that oxidative damage directly and predominantly contributes to fibrosis progression beyond conventional clinical and biochemical parameters. Although SOD and GSH showed significant associations with fibrosis in univariate analysis, their loss of significance in the multivariate model may indicate that their reduction is secondary to the overall oxidative burden rather than acting as independent determinants of fibrosis severity [11,12].

These findings are consistent with previous studies that have highlighted the central role of oxidative stress in chronic liver diseases, in which persistent inflammation and viral replication promote ROS production and fibrogenesis. Therefore, combining oxidative stress biomarkers with non-invasive fibrosis scores may provide a more comprehensive assessment of disease severity and progression [13,14].

From a clinical perspective, the incorporation of oxidative stress biomarkers particularly MDA alongside conventional fibrosis scores may improve the early identification of advanced fibrosis and enhance patient risk stratification. This approach may also create opportunities for the development of antioxidant-based therapeutic strategies aimed at reducing disease progression [15,16].

Despite its strengths, the present study has several limitations. The cross-sectional design does not permit the establishment of causal relationships between oxidative stress and fibrosis progression [1,16]. In addition, the study was conducted in a limited number of centers, which may reduce the generalizability of the findings. Furthermore,

fibrosis staging was not directly validated using liver biopsy or advanced imaging techniques such as FibroScan.

Future longitudinal studies are needed to explore the temporal relationship between oxidative stress and fibrosis progression. Further research should also investigate the role of antioxidant supplementation in reducing fibrosis and improving clinical outcomes in patients with chronic hepatitis [13-16].

CONCLUSION

The present study demonstrated a strong positive relationship between oxidative stress and liver fibrosis in patients with chronic hepatitis B and C, with elevated MDA levels showing a positive association with fibrosis scores (FIB-4 and APRI), whereas antioxidant markers, including SOD and GSH, showed a negative relationship with fibrosis severity. Importantly, MDA was identified as an independent predictor of liver fibrosis. The results of this study indicate that oxidative stress is closely involved in both the development and advancement of liver fibrosis. Integrating biochemical markers of oxidative stress with established non-invasive fibrosis indices may enhance the precision of disease evaluation and facilitate timely identification of patients at risk, thereby allowing earlier and more targeted therapeutic intervention.

Conflict of Interest: The authors declare no conflicts of interest.

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Authors' Contributions: B.M. contributed to conceptualization, data collection, and manuscript drafting. A.Z. was responsible for study design, supervision, and critical revision of the manuscript. A.T. performed data analysis, interpretation of results, and manuscript editing. All authors approved the final version of the manuscript.

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Data Availability: The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

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