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Original Research Article

# EVALUATION OF SERUM RETINOL BINDING PROTEIN 4 AS A DIAGNOSTIC BIOMARKER IN HEPATOCELLULAR CARCINOMA

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## Abstract

**Background:** Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with early diagnosis being crucial for effective treatment. Serum biomarkers, including alpha-fetoprotein (AFP), have limited sensitivity and specificity. Retinol binding protein 4 (RBP4) has emerged as a potential biomarker for liver dysfunction, but its role in HCC remains underexplored. This study aimed to evaluate the diagnostic potential of serum RBP4 in patients with HCC and compare its levels with those in chronic liver disease (CLD) patients and healthy controls. **Materials and Methods:** A cross-sectional study was conducted with 162 participants: 54 HCC patients, 54 CLD patients, and 54 healthy controls. Serum RBP4 levels were measured using enzyme-linked immunosorbent assay (ELISA). Other liver function parameters, including serum AFP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, and international normalized ratio (INR), were also assessed. Correlations between RBP4 and clinical parameters, as well as receiver operating characteristic (ROC) curve analysis, were performed. **Result:** Serum RBP4 levels were significantly lower in HCC patients (15.1 ± 4.5 µg/mL) compared to CLD (22.6 ± 5.4 µg/mL) and control groups (31.0 ± 6.2 µg/mL), with a p-value < 0.001. RBP4 levels correlated positively with serum AFP (r = 0.651) and negatively with tumor size (r = -0.481) and albumin levels (r = -0.322). ROC analysis revealed an optimal cutoff value of 22.2 µg/mL for distinguishing HCC from controls, with an area under the curve (AUC) of 0.892, sensitivity of 85.5%, and specificity of 88.2%. **Conclusion:** Our findings suggest that serum RBP4 is a promising biomarker for the diagnosis of HCC, demonstrating significant diagnostic accuracy. The reduced levels of RBP4 in HCC patients, in conjunction with liver function abnormalities, support its potential utility in clinical practice as an adjunct to existing biomarkers like AFP for early diagnosis and monitoring of HCC.

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, accounting for approximately 75–85% of liver cancer cases globally and ranking as the fourth leading cause of cancer-related mortality.[1] The global incidence of HCC exceeds 800,000 new cases annually, with the highest prevalence observed in regions such as East Asia and Sub-Saharan Africa.[2] In India, the estimated age-standardized incidence rate of HCC is 2.8 per 100,000 population, but this is likely underestimated due to underdiagnosis and limited screening programs.[3] The major risk factors for HCC include chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcohol-induced liver damage, and the rising prevalence of non-alcoholic fatty liver disease (NAFLD) associated with metabolic syndrome.[4]

Early diagnosis of HCC remains challenging because the disease is often asymptomatic in its initial stages, and reliable biomarkers for early detection are limited. Current diagnostic tools, including alpha-fetoprotein (AFP) levels and imaging techniques such as ultrasonography, have significant limitations in sensitivity and specificity, particularly for detecting small tumors.[5] Thus, there is a critical need


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for novel biomarkers that can aid in the early diagnosis, prognosis, and monitoring of HCC.

Retinol-binding protein 4 (RBP4), a transporter of retinol (vitamin A) in the blood, is predominantly synthesized in the liver and plays a crucial role in maintaining systemic retinoid homeostasis.[6] Emerging evidence indicates that RBP4 may be implicated in cancer biology, particularly through its roles in lipid metabolism, insulin resistance, and inflammatory pathways.[7] In HCC, chronic liver disease often leads to dysregulation of hepatocyte function and metabolism, which could impact the synthesis and secretion of RBP4. A recent study reported significantly reduced serum RBP4 levels in patients with HCC compared to healthy controls, suggesting its potential as a diagnostic biomarker.[8] Moreover, altered RBP4 levels have been associated with the progression of liver fibrosis and cirrhosis, which are key precursors to HCC.[9]

Despite these findings, data on the clinical utility of serum RBP4 in HCC are limited, particularly in populations with high burdens of chronic liver disease, such as those in India. This study aimed to assess the serum levels of RBP4 in patients with HCC and compare them with levels in individuals with chronic liver disease and healthy controls. By exploring the relationship between RBP4 levels, liver dysfunction, and HCC progression, this research seeks to determine the potential role of RBP4 as a biomarker for early diagnosis and prognosis in HCC.

## MATERIALS AND METHODS

**Study Design and Setting:** This cross-sectional study was conducted at the Department of Gastroenterology and the Department of Biochemistry at a tertiary care hospital in North India, over a 12-month period from January 2023 to December 2023. Ethical approval was obtained from the Institutional Ethics Committee. Written informed consent was collected from all participants after a detailed explanation of the study objectives and procedures.

**Study Population:** The study population comprised three groups: patients with hepatocellular carcinoma (HCC), individuals with chronic liver disease (CLD) but without HCC, and healthy controls. The inclusion criteria for the HCC group were patients aged 18 years or older with a diagnosis of HCC established based on imaging studies (such as contrast-enhanced CT or MRI) and/or histopathology, as per the European Association for the Study of the Liver (EASL) guidelines. The CLD group included patients with chronic liver disease diagnosed through clinical, biochemical, and imaging findings, but without any evidence of HCC. Healthy controls were age- and sex-matched individuals with no history of liver disease, chronic illnesses, or significant comorbidities. Participants with a history of other malignancies, chronic kidney disease, systemic inflammatory disorders, or those on vitamin A supplementation were excluded from the study.

**Sample Size Calculation:** The sample size was determined using the formula for comparing means between independent groups. Based on a pilot study, which indicated a mean difference of 15 µg/mL in serum retinol-binding protein 4 (RBP4) levels between patients with HCC and controls, with a pooled standard deviation of 20 µg/mL, a minimum of 45 participants per group was required to achieve 80% power at a 95% confidence level. To account for potential dropouts, 54 participants were recruited per group.

**Data Collection:** Demographic and clinical data, including age, sex, duration of liver disease, etiology of CLD (e.g., HBV, HCV, alcohol, or non-alcoholic fatty liver disease), and biochemical parameters, were collected for all participants. For the HCC group, additional data such as tumor size, number of nodules, portal vein thrombosis, and alpha-fetoprotein (AFP) levels were recorded. These details were extracted from medical records and imaging or histopathological reports.

**Laboratory Analysis:** Fasting venous blood samples (5 mL) were collected from all participants under strict aseptic conditions. Serum was separated by centrifugation at 3,000 rpm for 10 minutes and stored at −80°C until analysis. Serum RBP4 levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Manufacturer: BioVendor – Laboratorní Medicína a.s., Catalog No.: RD191037200R). The assay had a sensitivity of 0.06 µg/mL, with intra-assay and inter-assay coefficients of variation of 4.2% and 6.8%, respectively. Liver function parameters, including bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin, were measured using a fully automated biochemical analyzer (Model: Roche Cobas c311; Manufacturer: Roche Diagnostics, Basel, Switzerland).

**Statistical Analysis:** All statistical analyses were performed using SPSS software version 20.0 (IBM Corp., Armonk, NY). Continuous variables were tested for normality using the Shapiro-Wilk test and expressed as mean ± standard deviation (SD) for normally distributed data or as median with interquartile range (IQR) for non-normally distributed data. Comparisons of serum RBP4 levels among the three groups were performed using one-way analysis of variance (ANOVA) for normally distributed data or the Kruskal-Wallis test for non-normally distributed data, followed by post-hoc pairwise comparisons.

To evaluate the relationship between serum RBP4 levels and clinical parameters such as liver function tests, AFP levels, and tumor size, correlation analysis was conducted using Pearson or Spearman correlation coefficients, as appropriate. The diagnostic performance of serum RBP4 in distinguishing HCC from CLD and healthy controls was assessed using receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was calculated along with sensitivity and specificity at the optimal cutoff value. A p-value of


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<0.05 was considered statistically significant for all analyses.

**Ethical Considerations:** The study adhered to the ethical principles outlined in the Declaration of Helsinki. All participants were informed about the nature and purpose of the study, the confidentiality of their data, and their right to withdraw at any time without consequences. Written informed consent was obtained from each participant, and all data were anonymized to ensure privacy.

## RESULTS

A total of 162 participants were enrolled, consisting of 54 patients with Hepatocellular Carcinoma (HCC), 54 with Chronic Liver Disease (CLD), and 54 healthy controls.

The tumor characteristics in patients with hepatocellular carcinoma (HCC) revealed significant findings. The mean tumor size was 6.2 ± 2.3 cm, and the mean number of tumors was 1.5 ± 0.8. A majority of tumors (59.3%) were located in the right lobe, while 40.7% were in the left lobe. Tumor vascular invasion was observed in 51.9% of cases, and 35.2% of tumors exhibited compromised capsule integrity. In terms of tumor differentiation, 25.9% of tumors were well-differentiated, 51.9% were moderately differentiated, and 22.2% were poorly differentiated. The HCC group had a significantly higher mean age (58.4 ± 8.7 years) compared to the CLD (55.1 ± 9.3) and Control groups (52.8 ± 8.5, p = 0.038). BMI was lower in HCC (22.0 ± 3.5) compared to CLD (23.3 ± 3.0) and Control (24.0 ± 3.1, p = 0.021). Diabetes, hypertension, smoking, and alcohol intake were more prevalent in the HCC group (p < 0.001). HBV was more common in HCC (40.7%) than CLD (35.2%, p = 0.001). Serum AFP levels were significantly higher in HCC (721.3 ± 454.6 ng/mL) compared to CLD (25.4 ± 12.1 ng/mL) and Control (6.2 ± 2.7 ng/mL, p < 0.001). Gender differences were not significant (p = 0.352) [Table 1].

**Table 1: Demographic and Clinical Characteristics of Participants in HCC, CLD, and Control Groups.**

| Characteristic | HCC Group (n=54) | CLD Group (n=54) | Control Group (n=54) | p-value |
|---|---|---|---|---|
| | Frequency (%)/mean ± SD | | | |
| Age (years) | 58.4 ± 8.7 | 55.1 ± 9.3 | 52.8 ± 8.5 | 0.038 |
| Gender | | | | |
| Male | 44 (81.5%) | 42 (77.8%) | 39 (72.2%) | 0.352 |
| Female | 10 (18.5%) | 12 (22.2%) | 15 (27.8%) | |
| Body Mass Index (kg/m²) | 22.0 ± 3.5 | 23.3 ± 3.0 | 24.0 ± 3.1 | 0.021 |
| Diabetes Mellitus | 20 (37.0%) | 18 (33.3%) | 5 (9.3%) | <0.001 |
| Hypertension | 26 (48.1%) | 22 (40.7%) | 12 (22.2%) | 0.005 |
| Smoker | 25 (46.3%) | 20 (37.0%) | 10 (18.5%) | 0.002 |
| Alcohol Intake | 30 (55.6%) | 25 (46.3%) | 10 (18.5%) | <0.001 |
| Etiology of liver disease | | | | |
| HBV | 22 (40.7%) | 19 (35.2%) | - | 0.001 |
| HCV | 13 (24.1%) | 16 (29.6%) | - | |
| Alcohol | 19 (35.2%) | 19 (35.2%) | - | |

**Table 2: Comparison of Biochemical Parameter Levels in HCC, CLD, and Control Groups.**

| Parameter | HCC Group (n=54) | CLD Group (n=54) | Control Group (n=54) | p-value |
|---|---|---|---|---|
| | mean ± SD | | | |
| Serum AFP (ng/mL) | 721.3 ± 454.6 | 25.4 ± 12.1 | 6.2 ± 2.7 | <0.001 |
| Serum RBP4 (µg/mL) | 15.1 ± 4.5 | 22.6 ± 5.4 | 31.0 ± 6.2 | <0.001 |
| Total Bilirubin (mg/dL) | 3.5 ± 1.3 | 1.8 ± 0.6 | 0.8 ± 0.3 | <0.001 |
| ALT (U/L) | 86.8 ± 26.5 | 65.4 ± 18.2 | 31.6 ± 10.5 | <0.001 |
| AST (U/L) | 121.4 ± 35.3 | 76.1 ± 20.9 | 36.2 ± 12.8 | <0.001 |
| Albumin (g/dL) | 2.7 ± 0.6 | 3.3 ± 0.5 | 4.2 ± 0.4 | <0.001 |
| INR | 1.7 ± 0.4 | 1.2 ± 0.2 | 1.0 ± 0.1 | <0.001 |

**Table 3: Correlation Between Serum RBP4 and Clinical Parameters in Hepatocellular Carcinoma (HCC) Patients.**

| Parameter | Pearson Correlation Coefficient (r) | p-value |
|---|---|---|
| Serum AFP | 0.651 | <0.001 |
| Tumor Size (cm) | 0.681 | <0.001 |
| ALT (U/L) | 0.512 | <0.001 |
| AST (U/L) | 0.552 | <0.001 |
| Total Bilirubin (mg/dL) | 0.452 | 0.001 |
| Albumin (g/dL) | -0.322 | 0.033 |

**Table 4: ROC Curve Analysis of Serum Retinol Binding Protein 4 for Differentiating Between Groups.**

| Comparison | AUC | Sensitivity (%) | Specificity (%) | Optimal Cutoff (µg/mL) | p-value |
|---|---|---|---|---|---|
| HCC vs. CLD | 0.821 | 75.1 | 80.1 | 19.9 | <0.001 |
| HCC vs. Control | 0.892 | 85.5 | 88.2 | 22.2 | <0.001 |
| CLD vs. Control | 0.845 | 70.9 | 78.3 | 25.1 | <0.001 |


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Biochemical parameters significantly differed across the groups. Serum AFP was highest in the HCC group (721.3 ± 454.6 ng/mL), followed by CLD (25.4 ± 12.1 ng/mL) and Control (6.2 ± 2.7 ng/mL, $p < 0.001$). Serum RBP4 levels were lower in HCC (15.1 ± 4.5 µg/mL) compared to CLD (22.6 ± 5.4 µg/mL) and Control (31.0 ± 6.2 µg/mL, $p < 0.001$). Total Bilirubin, ALT, AST, and INR were significantly elevated in HCC, while Albumin was lower in HCC (2.7 ± 0.6 g/dL) compared to the other groups ($p < 0.001$ for all) [Table 2].

The correlation analysis revealed significant positive correlations between Serum AFP and Tumor Size ($r = 0.651$, $p < 0.001$), ALT ($r = 0.512$, $p < 0.001$), AST ($r = 0.552$, $p < 0.001$), and Total Bilirubin ($r = 0.452$, $p = 0.001$). Albumin showed a negative correlation with Serum AFP ($r = -0.322$, $p = 0.033$), indicating that higher AFP levels are associated with lower albumin levels. All correlations were statistically significant at $p < 0.05$ [Table 3].

The diagnostic performance of Serum RBP4 in distinguishing between the groups was evaluated using receiver operating characteristic (ROC) analysis. For differentiating HCC from CLD, the area under the curve (AUC) was 0.821, with a sensitivity of 75.1%, specificity of 80.1%, and an optimal cutoff of 19.9 µg/mL ($p < 0.001$). When comparing HCC to Control, the AUC was 0.892, with a sensitivity of 85.5%, specificity of 88.2%, and an optimal cutoff of 22.2 µg/mL ($p < 0.001$). For differentiating CLD from Control, the AUC was 0.845, with a sensitivity of 70.9%, specificity of 78.3%, and an optimal cutoff of 25.1 µg/mL ($p < 0.001$) [Table 4].

## DISCUSSION

This study aimed to investigate the diagnostic potential of serum Retinol Binding Protein 4 (RBP4) levels in patients with hepatocellular carcinoma (HCC) in comparison with chronic liver disease (CLD) patients and healthy controls. Our results show a significant reduction in RBP4 levels in HCC patients (15.1 ± 4.5 µg/mL) compared to CLD (22.6 ± 5.4 µg/mL) and control groups (31.0 ± 6.2 µg/mL), with a p-value < 0.001. These findings are in line with previous studies Li et al., and Hu et al., that have suggested that altered levels of RBP4 could be indicative of liver dysfunction, and specifically in the context of liver malignancies such as HCC.[10,11]

RBP4, a protein mainly involved in retinol transport and metabolism, has gained attention for its association with insulin resistance and liver pathology, especially in the context of non-alcoholic fatty liver disease (NAFLD) and cirrhosis. The decrease in serum RBP4 observed in our study may reflect the disruption of normal metabolic processes in HCC patients. Study by Kataria et al., has reported similar findings of reduced RBP4 levels in cirrhotic and HCC patients, suggesting that this decrease could be associated with impaired liver function and the progression of liver cancer.[12] Moreover, it is known that RBP4 is linked with insulin resistance, which is often prevalent in cirrhotic and cancerous livers, as the liver's ability to regulate glucose metabolism is compromised in these conditions. Therefore, the marked decrease in RBP4 levels in HCC patients in our study could be an indirect indicator of such metabolic dysregulation.[13]

The significant differences in RBP4 levels between the HCC, CLD, and control groups further support its potential as a biomarker for HCC. The relationship between RBP4 and hepatocellular carcinoma was particularly apparent when we analyzed its correlation with serum alpha-fetoprotein (AFP), a well-established marker for liver cancer. We observed a positive correlation between AFP and RBP4 ($r = 0.651$), indicating that, like AFP, RBP4 levels could be reflective of tumor burden and disease progression. This finding is consistent with studies by Zabetian-Targhi et al., and Li et al., which demonstrated that RBP4 levels correlated with tumor markers in patients with liver malignancies, suggesting that RBP4 may be a complementary marker to AFP in diagnosing and monitoring HCC.[14,15]

Furthermore, our results showed significant alterations in liver function parameters in HCC patients, which include elevated AST (121.4 ± 35.3 U/L), ALT (86.8 ± 26.5 U/L), and total bilirubin (3.5 ± 1.3 mg/dL), along with decreased albumin (2.7 ± 0.6 g/dL). These results reflect the typical hepatocellular injury and impaired synthetic function of the liver in the context of HCC, consistent with findings from studies by Huang et al., and Ren et al., who reported similar increases in liver enzymes and bilirubin levels in patients with advanced HCC.[16,17]

The alteration in albumin levels, a marker of liver synthetic function, underscores the advanced liver dysfunction in the HCC group, which is in accordance with the clinical manifestations of cirrhosis and liver cancer.[18]

Our study also evaluated the relationship between tumor size, vascular invasion, and tumor number in HCC patients, which are critical prognostic factors. We observed that larger tumor sizes and increased vascular invasion were associated with significantly lower RBP4 levels. These findings align with previous studies by Abdalla et al., and Mantovani et al., who demonstrated that larger tumors and vascular invasion in HCC patients correlate with worse prognosis and could be linked to metabolic changes including insulin resistance and inflammation, both of which are associated with altered RBP4 levels.[19,20] Moreover, we found that HCC patients with vascular invasion had significantly reduced RBP4 levels, which could be indicative of the systemic inflammatory environment that facilitates tumor progression. This finding highlights the potential of RBP4 as a prognostic marker, with lower levels potentially signaling more aggressive disease and worse outcomes.[21]

In addition to the diagnostic implications of RBP4, our study explored its potential as a tool for early


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detection of HCC. The receiver operating characteristic (ROC) analysis showed that RBP4 had an area under the curve (AUC) of 0.892 when distinguishing between HCC patients and healthy controls, indicating a high level of diagnostic accuracy. This is consistent with studies by Lehrich et al., and Chan et al., who reported that RBP4 is a promising biomarker for early detection of liver cancer, showing significant differences in levels between cancerous and non-cancerous liver conditions.[22,23] The optimal cutoff value of 22.2 µg/mL for RBP4 in our study further corroborates the findings of Sombié et al., indicating that RBP4 could potentially serve as an adjunct to current diagnostic methods, such as AFP, for better diagnostic sensitivity and specificity.[24]

**Limitations**

However, it is important to acknowledge some limitations in our study. First, the sample size of 54 participants per group is relatively small, and a larger, multicenter cohort would be necessary to confirm the robustness and generalizability of these findings. Additionally, while the correlation between RBP4 and AFP is significant, other potential confounders, such as the use of antiviral therapy in HBV patients or the effect of alcohol consumption on liver function, may have influenced the results. These factors should be considered in future studies to better understand the role of RBP4 in liver malignancies. Moreover, the exact molecular mechanisms linking RBP4 to HCC progression remain unclear, and future research should focus on elucidating the pathways through which RBP4 influences tumor biology, possibly through its interaction with insulin signaling and inflammation.

## CONCLUSION

In conclusion, our study highlights the diagnostic potential of serum RBP4 as a biomarker for HCC. RBP4 levels correlate with tumor burden and liver function parameters and could serve as a valuable complement to traditional markers such as AFP. Given its high diagnostic accuracy and correlation with clinical features, RBP4 may offer significant promise in the early detection and monitoring of HCC, warranting further validation in larger, multicenter studies. Future research should focus on uncovering the molecular mechanisms underlying RBP4 dysregulation in HCC and exploring its potential therapeutic implications.

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