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ORIGINAL ARTICLE

Predictive Value of Serum Fetuin-A in the Assessment of Disease Severity in Alcoholic Liver Cirrhosis

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Abstract

Background: Alcohol-related liver cirrhosis is a major cause of illness and death worldwide. Fetuin-A (also called AHSG) is a protein made by liver cells. Its level falls during inflammation and liver damage, so it can show how well the liver is functioning. This study measured serum Fetuin-A levels in patients with alcoholic liver cirrhosis, compared them with Child-Pugh (CP) stages, and studied their relationship with routine liver tests and C-reactive protein (CRP). **Methods:** This was a hospital-based cross-sectional analytical study with a control group done at Coimbatore Medical College & Hospital from March to August 2019. A total of 50 patients with alcoholic liver cirrhosis and 50 age-matched healthy individuals were included. Serum Fetuin-A levels were measured using sandwich ELISA. Liver function tests, CRP, prothrombin time/INR, and serum albumin were also measured. Disease severity was graded using the Child-Pugh scoring system. Statistical analysis was done using Student's t-test and Pearson correlation, with $p < 0.05$ considered significant. **Results:** Serum Fetuin-A levels were much lower in cirrhosis patients at 41.80 ± 33.82 ng/mL compared to healthy controls at 95.77 ± 10.11 ng/mL with a significant difference. Levels decreased as disease severity increased: CP-A 92.39 ± 32.11 ng/mL, CP-B 56.95 ± 8.92 ng/mL, and CP-C 13.71 ± 3.48 ng/mL, with all comparisons showing strong significance. Fetuin-A showed a strong negative correlation with total bilirubin, SGOT, SGPT, and CRP, meaning levels decreased as these increased. It showed a positive correlation with total protein and albumin, meaning levels increased along with better liver function. All these correlations were statistically significant. **Conclusion:** Serum Fetuin-A levels decrease steadily as liver function worsens in alcoholic cirrhosis. It shows strong relationships with common liver injury markers and inflammation, making it a useful marker to assess disease severity.

Keywords: Fetuin-A, AHSG, Alcoholic Liver Cirrhosis, Child-Pugh Score, C-Reactive Protein, Liver Biomarker

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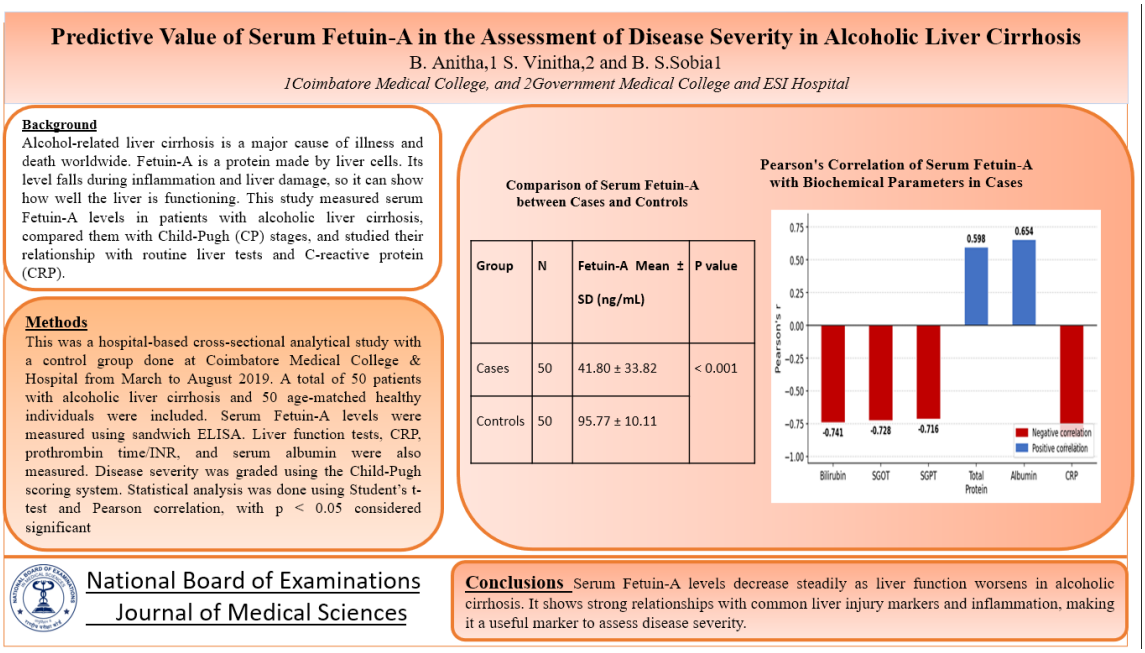
Graphical Abstract



Introduction

Alcoholic liver disease (ALD) includes a range of liver damage, starting from simple fat accumulation in the liver, progressing to alcoholic hepatitis, and finally to irreversible cirrhosis. It remains a major global health problem [1]. Worldwide, liver disease causes about two million deaths each year, which is about 4% of all deaths [2]. In India, alcohol is the most common cause of cirrhosis in adults, responsible for 43.2% of cases as shown in a recent national review and meta-analysis [3].

Even with progress in hepatology, the assessment of severity in alcoholic cirrhosis still mainly depends on scoring systems such as the Child-Pugh classification and the Model for End-Stage Liver Disease score. A single blood marker that can reflect both liver synthetic function and inflammation would be very useful in clinical practice.

Fetuin-A (also called AHSG) is a 59 kDa protein mainly produced by liver cells, contributing to more than 95% of its levels in the blood in adults [4]. It is coded by the AHSG gene on chromosome 3q27 and has several functions, including preventing abnormal calcification, acting as a negative acute phase reactant, inhibiting insulin receptor activity, and regulating TGF-β signalling [5]. Its levels decrease when inflammatory cytokines such as IL-1, IL-6, and TNF-α increase, and it also falls significantly when the liver's synthetic function is impaired [6]. Earlier studies have shown reduced Fetuin-A levels in primary biliary cirrhosis, chronic hepatitis, and liver cancer, and low levels are associated with poor short-term outcomes in advanced liver disease [7].

However, there are limited studies that specifically evaluate Fetuin-A as a marker of severity across different Child-Pugh stages in alcoholic cirrhosis. Therefore, this study was conducted to determine serum Fetuin-A levels in alcoholic cirrhosis and compare them with healthy individuals, to correlate Fetuin-A with disease severity using the Child-Pugh classification, and to study its relationship

with liver function test parameters and CRP.

Materials and Methods

Study Design and Setting

This was a hospital-based cross-sectional analytical study with a control group carried out in the Department of Biochemistry at Coimbatore Medical College & Hospital, Tamil Nadu, India, over a period of six months. Approval was obtained from the Institutional Ethics Committee, and written informed consent was taken from all participants.

Study Population

Fifty patients diagnosed with alcoholic liver cirrhosis were included from the Medical Gastroenterology outpatient and inpatient departments. Diagnosis was based on a history of long-term alcohol intake, abnormal liver function tests, and ultrasound findings.

Fifty healthy individuals of similar age, with no liver disease, were selected from the Master Health Check-Up programme as controls. A formal a priori sample size calculation was not performed. The study was conducted over a predefined study period, and all eligible patients with alcoholic liver cirrhosis and age-matched healthy controls presenting during this period were consecutively included.

Selection Criteria

Inclusion

Patients with confirmed alcoholic liver cirrhosis and age above 18 years.

Exclusion

Patients with non-alcoholic cirrhosis, age below 18 years, or those having diabetes, hypertension, heart failure, or chronic kidney disease. Patients with hepatorenal or hepatopulmonary syndrome were also excluded.

Sample Collection and Biochemical Estimation

Six millilitres of venous blood was collected under sterile conditions. Out of this, 4 mL was used for serum separation by centrifugation at 2000 rpm for 15 minutes. A portion was stored at −20°C for Fetuin-A estimation, and the remaining serum was used for liver function tests within 6 hours. Another 2 mL was collected in sodium citrate for coagulation studies. Serum Fetuin-A was measured using sandwich ELISA with a commercial kit. The test involved antibody-coated plates, enzyme-linked detection, and measurement of absorbance at 450 nm. C-Reactive Protein was measured using a quantitative turbidimetric method, with normal values up to 6 mg/L. Liver function tests included total bilirubin, AST, ALT, ALP, total protein, and albumin, measured using standard methods on a fully automated analyser. Coagulation tests included prothrombin time and activated partial thromboplastin time, with INR calculated.

Disease Severity Assessment

All patients were clinically examined for ascites and hepatic encephalopathy using standard criteria. Disease severity was graded using the Child-Pugh classification into Class A, Class B, and Class C based on scoring.

Statistical Analysis

Data analysis was done using SPSS version 20. Continuous values were expressed as mean and standard deviation. Student's t-test was used to compare two groups. One-way ANOVA with post-hoc tests was used to compare between different

Child-Pugh classes. Pearson correlation was used to study relationships between variables. A p value less than 0.05 was considered statistically significant.

Results

Demographic Profile

The average age was 47.26 ± 8.59 years in the patient group and 45.58 ± 10.53 years in the control group, and the difference was not statistically significant with p = 0.36, showing both groups were similar in age. Most of the patients were men at 96%, compared to 70% in the control group, which reflects the higher alcohol use among men in this region (Table 1).

Table 1. Age Comparison between Cases and Controls

Group	N	Mean ± SD (years)	t value	P value
Cases	50	47.26 ± 8.59	2.98	0.36 (NS)
Controls	50	45.58 ± 10.53		

NS = Not significant

Serum Fetuin-A: Cases vs Controls

Serum Fetuin-A levels were much lower in cirrhosis patients at 41.80 ± 33.82 ng/mL compared to 95.77 ± 10.11 ng/mL in healthy controls, and this difference was highly significant with t = −10.81 and p < 0.001. The mean difference was −53.97 ng/mL. This shows that as liver function decreases in cirrhosis, Fetuin-A levels also fall markedly (Table 2).

Table 2. Comparison of Serum Fetuin-A between Cases and Controls

Group	N	Fetuin-A Mean ± SD (ng/mL)	t value	P value
Cases	50	41.80 ± 33.82	−10.81	< 0.001
Controls	50	95.77 ± 10.11		

Liver Function Test Parameters

All liver function test values were significantly abnormal in patients compared to controls, with p < 0.001 for all. Total bilirubin was much higher in patients at 8.18 ± 7.41 mg/dL compared to 0.59 ± 0.20 mg/dL in controls. SGOT and SGPT levels were increased about 6 times and 5 times respectively. Total protein and albumin levels were clearly lower in patients, showing reduced liver synthetic function (Table 3).

Table 3. Comparison of Liver Function Test Parameters between Cases and Controls

Parameter	Cases Mean ± SD	Controls Mean ± SD	t value	P value
Total Bilirubin (mg/dL)	8.18 ± 7.41	0.59 ± 0.20	7.22	< 0.001
SGOT/AST (U/L)	132.72 ± 96.22	21.40 ± 4.88	8.17	< 0.001
SGPT/ALT (U/L)	107.80 ± 86.22	20.82 ± 8.08	7.10	< 0.001
ALP (U/L)	160.48 ± 74.94	79.04 ± 25.06	7.28	< 0.001
Total Protein (g/dL)	5.87 ± 1.25	7.40 ± 0.36	−8.27	< 0.001
Serum Albumin (g/dL)	2.72 ± 0.78	4.33 ± 0.94	−9.25	< 0.001

C-Reactive Protein

Serum CRP levels were much higher in patients at 52.48 ± 34.11 mg/L compared to 2.69 ± 2.21 mg/L in controls, and this difference was highly significant with $t = 10.29$ and $p < 0.001$. This shows that alcoholic cirrhosis is associated with a strong systemic inflammatory state (Table 4).

Table 4. Comparison of C-Reactive Protein (CRP) between Groups

Group	N	CRP Mean ± SD (mg/L)	t value	P value
Cases	50	52.48 ± 34.11	10.29	< 0.001
Controls	50	2.69 ± 2.21		

Fetuin-A across Child-Pugh Classes

Among the 50 patients, 8 patients had CP-A, 16 had CP-B, and 26 had CP-C. Serum Fetuin-A levels decreased as disease severity increased: 92.39 ± 32.11 ng/mL in CP-A, 56.95 ± 8.92 ng/mL in CP-B, and 13.71 ± 3.48 ng/mL in CP-C. All comparisons between the groups were highly significant with $p < 0.001$. This shows that Fetuin-A levels fall as liver disease becomes more severe (Table 5).

Table 5. Serum Fetuin-A Levels across Child-Pugh Classes in Cases

CP Class	**N (%)**	**Fetuin-A Mean ± SD (ng/mL)**	**Pairwise Comparison**	**P value**
CP-A	8 (16%)	92.39 ± 32.11	CP-A vs CP-B	< 0.001
CP-B	16 (32%)	56.95 ± 8.92	CP-A vs CP-C	< 0.001
CP-C	26 (52%)	13.71 ± 3.48	CP-B vs CP-C	< 0.001

Correlation of Fetuin-A with LFT and CRP

Fetuin-A levels showed a strong negative correlation with total bilirubin, SGOT, SGPT, and CRP, meaning that as these values increased, Fetuin-A levels decreased. It also showed a positive correlation with total protein and albumin, meaning that higher Fetuin-A levels were seen with better liver function. The strongest negative correlation was with CRP at $r = -0.853$, showing a clear opposite relationship between Fetuin-A and CRP (Table 6 and Figure 1).

Table 6. Pearson's Correlation Coefficients of Serum Fetuin-A with Biochemical Parameters in Cases

Parameter	**Pearson r**	**P value**
Total Bilirubin	−0.741	< 0.001
SGOT (AST)	−0.728	< 0.001
SGPT (ALT)	−0.716	< 0.001
Total Protein	+0.598	< 0.001
Serum Albumin	+0.654	< 0.001
C-Reactive Protein (CRP)	−0.853	< 0.001

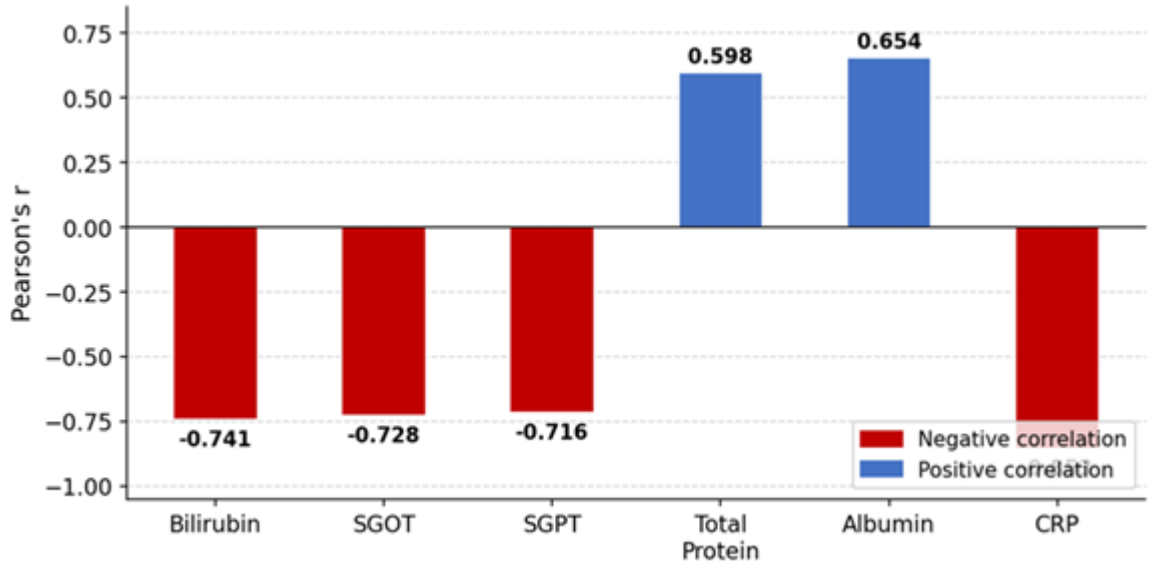


Figure 1. Pearson's Correlation of Serum Fetuin-A with Biochemical Parameters in Cases (all $p < 0.001$). Red bars = negative correlation; blue bars = positive correlation.

Discussion

The present study shows that serum Fetuin-A levels are much lower in patients with alcoholic liver cirrhosis and decrease further as the disease becomes more severe based on the Child-Pugh classification. These findings show that Fetuin-A can act as a marker for both reduced liver function and increased inflammation in these patients.

Fetuin-A is mainly produced by liver cells, with more than 95% of its level in the blood coming from the liver [4]. It is a negative acute phase reactant, which means its production decreases during inflammation. In cirrhosis, inflammatory cytokines such as IL-1, IL-6, and TNF-α increase and reduce Fetuin-A production [8]. The low Fetuin-A levels seen in cirrhosis patients in this study can be explained by both poor liver function and reduced production due to inflammation.

The decrease in Fetuin-A from CP-A to CP-C stages in this study is similar to earlier studies. Prystupa et al. [9] and Köklü et al. [10] also found that Fetuin-A levels are lower in more advanced stages of alcoholic liver disease, supporting its role as a marker of disease severity. Kalabay et al. [7] showed that very low Fetuin-A levels are linked to poor survival in alcoholic cirrhosis and can be compared with Child-Pugh and MELD scores. Their earlier study also showed that Fetuin-A reflects liver cell function and survival [11]. The current study supports these findings in an Indian population, where alcohol is a major cause of cirrhosis [3].

The strong negative relationship between Fetuin-A and CRP shows that as inflammation increases, Fetuin-A decreases. CRP increases in response to inflammation, while Fetuin-A decreases, showing an opposite pattern. Previous studies have also shown that high CRP is associated with worse outcomes in cirrhosis [12,13]. Fetuin-A also showed negative correlation with bilirubin, SGOT, and SGPT, and positive correlation with total protein and albumin. This means that as liver damage increases and liver function worsens, Fetuin-A levels decrease. Similar

findings have been reported in other studies [14–16].

Recent studies have also shown that Fetuin-A may play a role in the disease process itself. Chen et al. [17] found that Fetuin-A can affect inflammation and immune responses in alcoholic liver disease. Other studies have also described its role in controlling inflammation and tissue stress [18].

Globally, cirrhosis is a major cause of death, with alcohol being one of the leading causes worldwide and in India [19–21]. Fetuin-A, which can be measured easily using ELISA, may be a useful and affordable marker that reflects both liver function and inflammation in a single test. The global prevalence of alcohol-related liver disease is about 4.8%, with cirrhosis forming a significant part of it [22].

Patients with common comorbidities such as diabetes and hypertension were excluded to minimize metabolic and inflammatory confounding; however, this may limit the generalizability of the findings to the broader cirrhosis population where such conditions are prevalent. Potential confounding factors such as body mass index, nutritional status, smoking, and other subclinical inflammatory conditions were not assessed in this study and may have influenced serum Fetuin-A levels. This should be considered while interpreting the observed associations.

Although a formal a priori sample size estimation was not undertaken, the study demonstrated a large and statistically significant difference in serum Fetuin-A levels between cases and controls. This suggests that the sample size was adequate to detect meaningful differences for the primary outcome. However, this inference is based on post hoc assessment and should be interpreted cautiously.

Conclusion

This study demonstrates that serum Fetuin-A levels decrease significantly with increasing severity of alcoholic liver cirrhosis and show strong correlations with established biochemical markers of liver dysfunction and inflammation. These findings highlight the potential of Fetuin-A as a simple, non-invasive biomarker reflecting both hepatic synthetic function and systemic inflammatory status. Incorporating Fetuin-A into clinical assessment may aid in better stratification of disease severity alongside conventional scoring systems. Further large-scale and longitudinal studies are warranted to validate its prognostic utility and clinical applicability.

Limitations

The absence of a priori sample size estimation and reliance on a time-bound sample may affect the precision of the findings. Potential residual confounding cannot be excluded, as factors such as nutritional status, body composition, smoking, and other inflammatory conditions were not comprehensively evaluated. Additionally, the exclusion of patients with common comorbidities and the skewed distribution of patients across Child-Pugh classes, with a predominance of advanced disease (CP-C), may have influenced severity comparisons and limits the generalizability of these findings across all stages of cirrhosis. A degree of selection bias may also be present due to imbalance in gender distribution between cases and controls. Due to the sample size and study design, multivariable adjustment was not performed.

Future Scope

Longitudinal evaluation of Fetuin-A as a prognostic marker for decompensation events and mortality; comparative studies across non-alcoholic aetiologies of cirrhosis; genetic studies on AHSG gene expression modulation in ALD.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

No funding was received for conducting this study.

Data availability statement

The datasets generated and analysed in this study are available from the corresponding author on reasonable request. They are not publicly shared because they contain sensitive information that could indirectly identify participants.

Ethical Approval

This study has been approved by the Institutional Human Ethics Committee of Coimbatore Medical College, Coimbatore carrying certificate number 0173/2018, dt 15.12.2018

Informed Consent

Written informed consent was obtained from all participants after explaining the study procedures, potential risks and benefits. Consent covered both participation and publication of anonymised findings, with assurance of confidentiality and data privacy.

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