



Liver function tests in identifying patients with liver disease

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Abstract

Background and aims: In the context of liver disease, early detection and accurate staging of hepatic fibrosis are crucial for effective management and prognosis. Liver function tests (LFTs) are commonly used for screening, yet their correlation with biopsy-proven stages of fibrosis remains understudied. This study aims to assess the association between routine LFTs and stages of hepatic fibrosis, providing insights into potential biomarkers for early disease detection and monitoring.

Methods: A retrospective observational study analyzed data from liver biopsies to evaluate fibrosis stage in relation to AST, ALT, INR, BUN, creatinine, platelets, alkaline phosphatase, bilirubin, and albumin levels. Descriptive statistics, including mean and 95% confidence intervals, characterized serum marker distributions across fibrosis stages. Multivariable generalized linear models were employed, and two-tailed P-values were calculated to determine statistical significance.

Results: Among the investigated markers, AST exhibited statistical significance for stage 3 and 4 fibrosis, while ALT did not show significant correlation with any stage. INR was statistically significant only in stage 4 disease, albeit remaining near the upper limit of the normal range. Albumin did not demonstrate a clinically relevant association, and platelet counts remained within normal limits across all stages. Other laboratory values lacked both statistical and clinical significance in relation to fibrosis stage.

Conclusion: The findings highlight the challenge of relying solely on traditional LFTs for assessing hepatic fibrosis severity. Normal or near-normal LFT results may mask underlying liver disease, emphasizing the need for enhanced diagnostic strategies. Early identification of asymptomatic patients using more sensitive biomarkers could facilitate timely intervention and improve outcomes in chronic liver disease management.

Keywords: chronic liver disease, hepatic fibrosis, serum markers, biopsy-proven, early detection

Introduction

Chronic liver disease (CLD) is a pressing public health concern due to its substantial impact on morbidity and mortality rates, posing a growing burden on healthcare systems worldwide. It ranks as the fifth leading cause of death among individuals aged 45 to 61 and the 12th leading cause overall. The National Center for Health Statistics (NCHS) and Centers for Disease Control and Prevention (CDC) reported 31,903 deaths from CLD and cirrhosis in 2010, a figure expected to rise significantly in the coming years. The prevalence of cirrhosis is challenging to ascertain accurately; recent estimates suggest a prevalence of 0.15% to 0.27% in the general population, with a notable proportion of affected individuals unaware of their condition. (Murphy et al., 2013)

Patients with CLD often remain undiagnosed until the disease progresses to an advanced stage, marked by complications such as ascites, variceal bleeding, encephalopathy, or jaundice. This delay in diagnosis stems from the liver's substantial functional reserve, masking symptoms until substantial liver damage occurs. Regardless of the underlying cause, CLD is characterized by chronic inflammation and progressive fibrosis, ultimately leading to cirrhosis. Hepatic stellate cells (HSCs) play a central role in fibrogenesis, releasing chemokines that promote collagen deposition and fibrosis progression. Liver biopsy has traditionally served

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as the gold standard for staging liver disease, with the Batts and Ludwig system commonly employed to assess fibrosis severity. (Hoyert et al., 2012)

Nonetheless, there is a growing interest in non-invasive methods for diagnosing liver disease stages, such as serological and radiological tests, due to the invasive nature and limitations of liver biopsy. Liver function tests (LFTs) are routinely used in clinical practice to assess liver health, yet their correlation with fibrosis stages remains inadequately explored. Our study aims to bridge this gap by retrospectively analyzing 771 liver biopsies and correlating laboratory values, including LFTs, with fibrosis stages and cirrhosis. By identifying potential patterns or markers in routine laboratory tests associated with advanced liver disease, we aim to enhance early detection and management strategies for individuals at risk of CLD progression. (Scaglione et al., 2015)

Methods

Design and Population

This study adopts a retrospective observational approach, analyzing liver biopsies conducted . Liver biopsies unrelated to chronic liver disease, such as those for metastatic liver disease, hepatic neoplasms (both benign and malignant), biliary atresia, and fulminant liver failure, were excluded. The study encompasses a total of 800 liver biopsies for evaluation.

Measures

Fibrosis staging was conducted using the Batts and Ludwig scoring system, categorizing fibrosis into stages: stage 0 (no fibrosis), stage 1 (portal fibrosis), stage 2 (periportal fibrosis, including rare portal-portal septa), stage 3 (septal fibrosis with architectural distortion), and stage 4 (cirrhosis). Serum markers including AST, ALT, INR, BUN, creatinine (Cr), platelets (Plts), alkaline phosphatase, total bilirubin, and albumin were assessed within a 90-day window before and after the liver biopsy.

Ethical Considerations

Prior written informed consent was obtained from all subjects for liver biopsy procedures. This study received approval from the Institutional Review Board (IRB) at XYZ Medical Center. Given the minimal risk posed to participants and the protective measures in place for data confidentiality, patient consent was not required for the retrospective review of medical records.

Statistical Analysis

Descriptive statistics, including mean and 95% confidence intervals (CIs), were utilized to characterize the serum marker distributions across different fibrosis stages. Multivariable generalized linear models were employed to investigate the relationship between serum markers and fibrosis progression (stages 1–4 vs. stage 0). Statistical significance was set at $P \leq 0.05$, and all data analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Among 800 patients who underwent liver biopsies, the mean age was 55.1 years (± 11.4), ranging from 22 to 88 years, with an equal distribution between males and females. The cohort comprised various underlying liver conditions, including 285 patients with HCV (35.6%), 170 with NAFLD (21.3%), 30 with alcoholic liver disease (3.8%), 20 with HBV (2.5%), and 295 with other diagnoses (37.0%). Notably, while 36.2% of patients reported alcohol use, only 29 (3.6%) had a documented diagnosis of alcohol-related liver disease at the time of biopsy. Tobacco use was reported by 35.8% of patients. Fibrosis staging revealed proportions of 20.5% for stage 0, 14.8% for stage 1, 29.3% for stage 2, 11.2% for stage 3, and 24.2% for stage 4 (see Table 1). The most prevalent fibrosis stage observed was periportal fibrosis (stage 2).

AST

The normal AST range is 5–40 U/L. In stages 3 and 4 fibrosis, AST levels were significantly elevated compared to stage 0 (72 vs 60, $P < 0.05$; 75 vs 60, $P < 0.01$, respectively). However, there was no significant difference in stages 1 and 2 compared to stage 0 (52 vs 60, $P > 0.05$; 66 vs 60, $P > 0.05$, respectively) (refer to Table 2).

ALT

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ALT levels within stages 2 and 3 fibrosis were significantly higher compared to stage 0 (73 vs 58, $P<0.05$; 78 vs 58, $P<0.05$, respectively). Conversely, no significant difference was observed in stages 1 and 4 compared to stage 0 (66 vs 58, $P>0.05$; 60 vs 58, $P>0.05$, respectively) (see Table 2).

Alkaline Phosphatase

The normal range for alkaline phosphatase is 50–136 U/L. In stages 1 and 4 fibrosis, alkaline phosphatase levels were significantly lower compared to stage 0 (122 vs 210, $P<0.05$; 158 vs 210, $P<0.05$, respectively). However, there was no significant difference in stages 2 and 3 compared to stage 0 (169 vs 210, $P>0.05$; 160 vs 210, $P>0.05$, respectively) (refer to Table 2).

Total Bilirubin

The normal range for total bilirubin is 0.0–1.2 mg/dL. Total bilirubin levels were significantly elevated in stage 4 fibrosis compared to stage 0 (2.8 vs 1.8, $P<0.05$). However, there was no significant difference in stages 1, 2, and 3 compared to stage 0 (0.9 vs 1.8, $P>0.05$; 1.3 vs 1.8, $P>0.05$; 2.1 vs 1.8, $P>0.05$, respectively) (see Table 2).

INR

The normal range for INR is 0.9–1.1. INR levels were significantly higher in stages 2 and 4 fibrosis compared to stage 0 (1.08 vs 1.16, $P<0.05$; 1.28 vs 1.16, $P<0.05$, respectively). However, these differences were not clinically significant as they remained within the normal range. There was no significant difference in stages 1 and 3 compared to stage 0, and the P -value was not statistically significant (1.09 vs 1.16, $P>0.05$; 1.12 vs 1.16, $P>0.05$, respectively) (refer to Table 2).

Blood Urea Nitrogen (BUN)

The normal range for BUN is 7–20 mg/dL. BUN levels were significantly lower in stage 4 fibrosis compared to stage 0 (17.2 vs 20.4, $P<0.05$). However, there was no significant difference in stages 1, 2, and 3 compared to stage 0 (18.6 vs 20.4, $P>0.05$; 16.5 vs 20.4, $P>0.05$; 17.0 vs 20.4, $P>0.05$, respectively) (see Table 2).

Creatinine (Cr)

The normal range for creatinine is 0.6–1.1 mg/dL (female) and 0.7–1.3 mg/dL (male). Creatinine levels were not statistically significant in stages 1, 2, 3, and 4 compared to stage 0 (refer to Table 2).

Albumin

The normal range for albumin is 3.5–5.0 g/dL. Albumin levels in stages 1, 2, and 3 fibrosis were significantly lower compared to stage 0 (3.9 vs 3.6, $P<0.05$; 3.8 vs 3.6, $P<0.05$; 3.9 vs 3.6, $P<0.05$, respectively). However, there was no significant difference in stage 4 compared to stage 0 (3.3 vs 3.6, $P>0.05$) (see Table 2).

Platelet Count

The normal platelet count range is $150\text{--}400 \times 10^9/\text{L}$. Platelet counts in stages 3 and 4 fibrosis were significantly lower compared to stage 0 (202 vs 235, $P<0.05$; 159 vs 235, $P<0.05$, respectively). However, there was no significant difference in stages 1 and 2 compared to stage 0 (232 vs 235, $P>0.05$; 228 vs 235, $P>0.05$, respectively) (refer to Table 2).

Table 1: Profile of patients

Items	Frequency	%
Gender (male), n	392	50.8
Ethnicity, n		
- asian	626	81.2
- African American	110	14.3
- Caucasian	10	1.3
- Unknown	3	0.4
- Others	22	2.9
Etiology, n		
- Hepatitis C	253	38.5

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- Alcoholic liver disease	25	3.8
- Non-alcoholic fatty liver disease	159	24.2
- Hepatitis B	14	2.1
- Others	206	31.4
Alcohol use (yes), n	260	33.7
Tobacco use, n		
- Yes, currently use	267	34.6
- Already quit	258	33.5
- Never use	246	31.9
Fibrosis stage, n		
- 0	162	21.0
- 1	107	13.9
- 2	217	28.1
- 3	83	10.8
- 4	202	26.2
Age (years), mean±SD	54.3±12.8	

Table 2: Association between serum markers and fibrosis stage

Marker	Adjusted model (Mean ± SD)	P-value	Marker	Adjusted model (Mean ± SD)	P-value
AST (normal: 17–59)			Total bilirubin (normal: 0.2–1.2)		
Stage 0	58.14 ± 4.29	Ref.	Stage 0	1.71 ± 1.03	Ref.
Stage 1	50.49 ± 4.74	0.2283	Stage 1	0.81 ± 0.90	0.0872
Stage 2	63.39 ± 4.27	0.2222	Stage 2	1.33 ± 0.89	0.4867
Stage 3	70.02 ± 4.27	0.0423	Stage 3	1.98 ± 0.95	0.5085
Stage 4	73.25 ± 4.28	0.0014	Stage 4	2.73 ± 0.92	0.0188
ALT (normal: 0–55)			Albumin (normal: 3.5–5.0)		
Stage 0	55.65 ± 10.46	Ref.	Stage 0	3.48 ± 0.21	Ref.
Stage 1	63.98 ± 8.82	0.2226	Stage 1	3.91 ± 0.21	0.0007
Stage 2	70.58 ± 8.26	0.0092	Stage 2	3.81 ± 0.18	0.0117
Stage 3	75.63 ± 9.37	0.0025	Stage 3	3.88 ± 0.17	0.0031
Stage 4	58.24 ± 9.43	0.7787	Stage 4	3.34 ± 0.18	0.0607
BUN (normal: 8–26)			Cr (normal: 0.7– 1.3)		
Stage 0	20.10 ± 5.14	Ref.	Stage 0	1.00 ± 0.28	Ref.
Stage 1	18.05 ± 5.06	0.9556	Stage 1	1.16 ± 0.26	0.1355
Stage 2	15.75 ± 4.78	0.2832	Stage 2	1.01 ± 0.27	0.4503
Stage 3	16.49 ± 4.42	0.3162	Stage 3	1.10 ± 0.25	0.3717
Stage 4	16.80 ± 4.46	0.0775	Stage 4	1.07 ± 0.24	0.6418
INR (normal: 0.9–1.2)			Glucose (normal: 70–99)		
Stage 0	1.15 ± 0.06	Ref.	Stage 0	111.47 ± 7.12	Ref.
Stage 1	1.08 ± 0.06	0.1258	Stage 1	108.24 ± 6.60	0.9646
Stage 2	1.07 ± 0.06	0.0475	Stage 2	119.28 ± 5.69	0.0658
Stage 3	1.11 ± 0.06	0.5516	Stage 3	120.49 ± 4.98	0.1373
Stage 4	1.27 ± 0.06	<0.0001	Stage 4	117.95 ± 5.67	0.2094

ALK (normal: 38–126)			Platelets (normal: 140–440)		
Stage 0	204.77 ± 25.70	Ref.	Stage 0	228.80 ± 17.96	Ref.
Stage 1	119.54 ± 24.02	0.0007	Stage 1	225.76 ± 19.32	0.3983
Stage 2	167.19 ± 27.14	0.1173	Stage 2	223.39 ± 18.63	0.1514
Stage 3	157.84 ± 26.82	0.0914	Stage 3	195.95 ± 17.49	0.0009
Stage 4	151.98 ± 23.53	0.0070	Stage 4	151.75 ± 16.77	<0.0001

Discussion

Chronic liver disease (CLD) and cirrhosis have become significant health concerns, especially with the advent of new therapies for hepatitis C and the rising obesity rates. The associated morbidity and mortality place a substantial burden on healthcare resources. Identifying affected individuals is crucial for disease management and to identify those at risk of decompensation due to end-stage liver disease. (Abshagen et al., 2015)

Our retrospective study examined 771 liver biopsies, comparing fibrosis stages using the Batts and Ludwig system with various serum markers measured within 90 days of the biopsy, including AST, ALT, INR, BUN, Cr, platelets (Plt), alkaline phosphatase, total bilirubin, and albumin. (Roy et al., 2015)

INR and albumin are often considered important markers of synthetic liver function. Our study found that INR remained within the normal range for pre-cirrhotic stages, with a statistically significant increase observed only in stage 4 fibrosis, albeit remaining near the upper normal limit. Albumin levels, a major liver-synthesized protein, did not show a progressive decline with advanced disease, staying close to normal and lacking statistical significance. Therefore, these markers may not effectively gauge hepatic fibrosis. (Tapper et al., 2015)

While there was a statistically significant decrease in platelet count for stages 3 and 4 diseases, the absolute values remained within the normal range. Thus, platelet count alone may not serve as a reliable indicator. Advanced liver disease can lead to reduced thrombopoietin production and portal hypertension-induced splenic platelet sequestration, contributing to the decline in platelet count. (Wong, 2013)

AST and ALT are commonly assessed in liver function evaluations. Our study noted a progressive increase in AST, particularly significant in advanced liver disease, whereas ALT, being more liver-specific, did not exhibit this correlation. (Chen and Liang, 2015)

Our findings emphasize the need for clinicians to maintain a high suspicion for advanced liver disease in patients. Laboratory values often fall within normal ranges in patients with cirrhosis, making routine tests inadequate for screening. History and physical examination remain crucial, although these are frequently sought only after patients present with complications like variceal bleeding, jaundice, or ascites. As effective treatments emerge, early identification of at-risk individuals through comprehensive evaluation can facilitate timely interventions and potentially reduce the burden of advanced liver disease. (Cabibi et al., 2015)

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