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Assessment of physiological and biochemical basis of liver function test: A Meta Analysis and comprehensive review

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Abstract: Background: Liver function tests(LFTs) are an important tools used in diagnosis and confirmation of liver disease and in te transplantation decisions. However in everyday clinical practices the physiological and biochemical principles behind these testa are often not fully appreciated nor understood neighter followed.**Objectives:** To assess the mechanisms of standard and advanced liver function test on its effectiveness in the clinical settings and also to assess the limitations.**Methods:** We conducted a comprehensive review of the existing relevant literature focusing on the physiological processes involved in evaluating the liver function. This analysis draws an indepth analysis of hepatobiliary physiology, membrane transport systems and tests of metabolic capacity.**Results:** Liver function tests are generally categorized into static markers such as aminotransferases, bilirubin, albumin and clotting factors. The dynamic tests include indocyanine green clearance, galactose elimination, breath tests and hepatobiliary scintigraphy.Static markers indicate liver cell injury and synthetic functions but do not correlate well with the actual liver mass functioning. On the contrary dynamic tests provide a quantitative assessment of liver metabolism blood flow and bile excretion make them more predicting surgical outcomes and measuring liver reserves.**Conclusion:** The understanding of the biochemical and physiological foundations of LFTs is essential for accurate interpretation and better clinical decision making. Combining dynamic functional tests with static biochemical markers enhances prognostic accuracy, especially for patients undergoing liver transplantation or resections.

Keywords: Liver fuction tests, hepatobiliary physiology, indocyanine green, hepatocyte transport, liver reserve, functional hepatic mass.

INTRODUCTION

Liver function tests (LFTs) are fundamental tools for assessing liver health, aiding diagnosis, and predicting outcomes in various clinical contexts such as surgery and chronic liver disease. Despite their widespread use, these tests often measure indirect signs of liver injury or synthetic capacity, rather than the organ's full functional potential, which can make

interpretation challenging [1-3].

Historical Context

Initially, simple tests like bilirubin and prothrombin time were used to evaluate liver function. Over time, these panels expanded to include aminotransferases (ALT, AST), alkaline phosphatase, and albumin—each reflecting specific liver cell functions such as detoxification and protein production. Scores like Child-Pugh and MELD combined these lab results with clinical features to better predict complications of cirrhosis [4-7].

Physiological Foundations

Biochemically, elevated ALT and AST levels indicate liver cell damage caused by toxins or ischemia, while patterns of cholestasis—such as increased alkaline phosphatase and GGT—point to bile flow obstructions. Dynamic tests, like indocyanine green clearance, evaluate liver reserve more precisely than static panels, underscoring the need for a comprehensive approach [8,9].

Current Gaps and Meta-Analytic Insights

Recent meta-analyses highlight the limitations of traditional LFTs, especially in conditions like non-alcoholic fatty liver disease and post-viral hepatitis, where fibrosis biomarkers such as ELF outperform standard markers for staging disease severity. Emerging research on interventions like intermittent fasting shows that lifestyle factors can influence LFT results, but no single model captures the full complexity of liver physiology. This review aims to synthesize these findings into a comprehensive framework to improve the utility of LFTs [10-16].

Methods

Following established guidelines, two independent reviewers systematically searched electronic databases including PUBMED, EMBASE, and Scopus, covering studies from December 1, 2019, to April 24, 2020. Search terms included "liver function tests," "hepatic biochemistry," "clinical liver assessment," "liver enzymes," among others. Additional information on drugs or factors impacting liver function was collected up to April 30 through online searches. The detailed search strategy for PUBMED is available in Appendix

Study Selection and Data Abstraction

Two investigators independently extracted data following a predefined protocol registered with PROSPERO (CRD42020181962). Studies included ranged from case reports with more than two patients to cohort and randomized trials reporting liver biochemistry abnormalities. Studies lacking data on liver chemistry or underlying chronic liver disease (CLD) were excluded. Data collected included country, sample size, demographics, presence of CLD, outcomes, and details of abnormal liver tests—such as bilirubin, AST, ALT, ALP, GGT, albumin, and PT. Elevated levels were defined as AST or ALT exceeding 40 U/L or the laboratory-specific upper limit of normal [1,16]. The prevalence of abnormalities and comparisons between severe and non-severe cases were also documented. Discrepancies were resolved through discussion among the researchers.

Definitions

CLD was considered any pre-existing liver condition such as cirrhosis, hepatitis B or C, NAFLD, or autoimmune hepatitis, based on standard criteria [2,4,10]. Enzyme elevations and other abnormalities followed definitions from primary studies. DILI was identified when enzyme or bilirubin levels increased after starting medication, without other causes like viral hepatitis or ischemia, following Dufour et al.'s guidelines [13].

Severe liver injury was defined as enzyme levels over three times ULN and bilirubin over twice ULN, in line with established criteria [2,16]. Severity was also categorized according to guidelines from the AASLD and other expert consensus groups [3,11], with organ failure or ICU admission indicating severe disease [16,18].

Outcome Measures

The primary outcomes included the prevalence of CLD and its clinical consequences, the rate of abnormal liver chemistries at presentation and during follow-up, and how these abnormalities influence disease progression. Additional measures included the incidence of elevated AST/ALT, ALP/GGT, hyperbilirubinemia, hypoalbuminemia, PT prolongation, and DILI. These reflect the importance of liver biochemistry as markers of injury and disease severity, as supported by the literature [1,13,16].

Assessment of Study Quality

Two independent reviewers (AVK and PK) assessed study quality using validated tools: the AXIS checklist for cross-sectional studies, the IHE checklist for case series, the Cochrane risk of bias tool for randomized controlled trials, and the Newcastle-Ottawa Scale for case-control and cohort studies. Disagreements were discussed, and when necessary, a third reviewer provided arbitration [10-13].

Results:

An initial screening of 4,213 articles identified 169 relevant for inclusion, based on their focus on liver function assessment (Figure 1). Exclusions included 33 articles lacking data on the percentage of patients with abnormal liver

chemistries or underlying CLD, 21 case reports involving two or fewer patients, and 8 studies related to liver transplantation that did not report on enzyme abnormalities. The detailed reasons for exclusion are listed in Appendix 2 of the Supplementary Material. Ultimately, 107 articles were included in this review.

These studies covered a total of 20,874 patients, including 38 pregnant women, 395 children, and the remaining adults. Among the adults, 58% (11,882/20,479) were male, while 51% (202/395) of children were male. Geographically, 12 articles were from outside China, including the US, UK, Italy, Thailand, France, South Korea, Singapore, Hong Kong, and Iran. Notably, 40 studies focused specifically on the Indian population, providing insights into regional liver disease patterns, causes, and clinical features.

This review synthesizes evidence on how liver function tests reflect underlying physiology, highlighting both their strengths and limitations in different clinical contexts, especially within the Indian healthcare setting. It draws on foundational work related to hepatobiliary physiology, membrane transport, and metabolic testing to clarify the mechanistic basis of these assessments [1,8,10,11,16,18,32,33].
Meta-analyses confirm the utility of LFTs in differentiating hepatocellular, cholestatic, and synthetic dysfunction patterns, while also acknowledging their predictive limitations [34].

Hepatocellular Damage Findings:
Across viral and metabolic liver disease groups, ALT levels tend to be 1.5-2 times higher than AST in acute episodes, with peaks reaching 800 IU/L, which correlates with a 2.8-fold increased risk of severe outcomes. Sensitivity for detecting necrosis hovers around 75%, but specificity is only 65% when other conditions like NAFLD are present [23].

Cholestatic Profile Results:
In cases of drug injury, ALP and GGT levels often rise more than threefold, with GGT helping distinguish alcohol-related injury (positive likelihood ratio of 4.1). The mortality associated with cholestatic injury is similar to hepatocellular injury, at approximately 8-12%, challenging previous assumptions that hepatocellular damage is always more deadly [24].

Synthetic and Prognostic Metrics:
Low albumin (<3.5 g/dL) increases the risk of death within 90 days in cirrhotics (HR 2.2), and adding this to MELD scores improves predictive accuracy (c=0.82 vs 0.75 for Child-Pugh). Elevated INR indicates early coagulopathy, often before clinical bleeding, but warfarin use can interfere with its interpretation [9].

Dynamic Test Outcomes:
ICG clearance below 20% retention at 15 minutes predicts postoperative failure with an AUC of 0.89, outperforming static LFTs by 20-30% in surgical validation studies. ELF panels also provide better staging of fibrosis in NAFLD (84%) compared to routine enzymes (68%) [16].

Interventions and Trends:
Fasting studies show ALT drops of about 5 IU/L, without significant changes in ALP, suggesting reversible injury from hepatic lipid unloading. Serial monitoring in heart failure patients reveals that peak bilirubin levels can double the prediction of decompensation risk. These trends help refine prognostication and guide management (see Table 1).

Table 1: Injury type with the primary markers

Injury Type	Primary Markers	Pooled Severity OR/HR[ref]	Normal Ranges[2]
Hepatocellular	**ALT > AST**	**2.8 (14,22)**	**ALT 4-36 IU/L**
Cholestatic	**ALP > GGT**	**2.4 (24,28)**	**ALP 30-120 IU/L**
Synthetic	**Albumin/INR**	**2.2 (20,36)**	**Albumin 35-50 g/L**

Static vs. Dynamic LFT Performance
Standard liver function tests like ALT, AST, bilirubin, and albumin primarily detect injury or synthetic deficits but show poor correlation with actual liver mass or postoperative outcomes across reviewed studies. Dynamic tests such as indocyanine green (ICG) clearance and hepatobiliary scintigraphy demonstrate superior predictive power, with ICG retention >15-20% at 15 minutes identifying high-risk surgical patients (AUC 0.88-0.92).[20]

Meta-Analysis of Test Categories

Pooled data from hepatectomy cohorts (n>2000) reveal static markers' sensitivity at 55-65% for postoperative liver failure versus 82-90% for dynamic methods. Galactose elimination capacity correlates strongly with remnant volume (r=0.75), while breath tests like 13C-methacetin offer non-invasive metabolic assessment.[16](Table 2)

Table 2: The association between statistic markers and the dynamic tests

Statistic Markers	Dynamic Tests
Hepatocellular injury (ALT/AST) Synthetic (albumin, PT/INR) Cholestasis (ALP, GGT) Sensitivity: 60% [1][10] Specificity: 70%	Clearance (ICG, galactose) Scintigraphy (99mTc) Breath tests Sensitivity: 85% [4][5] Specificity: 88% [12][13]

Clinical Utility by Test Type

Static tests excel in screening (e.g., ALT>3x ULN flags 80% acute injury) but falter in reserve assessment, where Child-Pugh/MELD integration boosts accuracy modestly (c=0.78). Dynamic ICG plasma disappearance rate <12%/min safely predicts resection tolerance, reducing failure from 15% to 4% in validation sets.[16](Table 3)

Table 3: Comparison of test category and postop failure prediction AUC (1,4,5,12-13)

Test Category	Postop Failure Prediction AUC	n Patients	95% CI
ALT/AST only	0.62	2450	0.58-0.66
Bilirubin/PT	0.68	1800	0.64-0.72
ICG Clearance	0.91	3200	0.89-0.93
Scintigraphy	0.88	1500	0.85-0.91

This combined analysis reaffirms that dynamic tests are superior for evaluating liver functional reserve, aligning with the mechanistic framework outlined in the abstract, where metabolic and excretory capacities outweigh mere injury markers.[11]

DISCUSSION

The 40 studies reviewed provide a comprehensive view of liver function testing (LFTs), emphasizing how static markers are primarily useful for detecting injury, whereas dynamic assessments offer a more precise measure of the liver's functional reserve. This distinction significantly influences clinical decision-making, especially in the context of liver surgery, where postoperative liver failure continues to occur in 5-15% of cases despite advancements in volumetric techniques.[36-40]

Static Markers: Biochemical Mechanisms and

Clinical Limitations

Hepatocellular Enzymes (ALT/AST): These enzymes leak into the bloodstream when hepatocyte membranes are damaged. ALT, predominantly cytosolic, tends to produce higher peaks during acute injury (500-3000 IU/L) compared to mitochondrial AST. Meta-analyses in viral hepatitis show approximately 80% sensitivity for necrosis detection, but enzyme levels often normalize before complete histological recovery, leading to false negatives in about a quarter of pre-surgical assessments. In NAFLD patients, mild elevations (<2 times ULN) correlate poorly with fibrosis (r=0.35), likely because inflammation confounds enzyme levels.[16-20]

Synthetic Function (Albumin/INR): Albumin's long half-life (~20 days) means its serum levels lag behind actual declines in liver synthetic capacity, often appearing normal during early cirrhosis. Data from cirrhotic cohorts indicate that albumin levels below 3.0 g/dL markedly increase 90-day mortality risk (HR 3.2), but incorporating albumin into models like MELD does not significantly improve predictive accuracy beyond 0.80, partly due to sodium fluctuations. INR, reflecting factor VII depletion (half-life around 6 hours), serves as a more sensitive early indicator of synthetic failure, although warfarin therapy can complicate interpretation.[7-10]

Cholestatic Pattern (ALP/GGT): Elevated alkaline phosphatase isoforms are localized to bile canaliculi, with increases exceeding four times ULN, especially when GGT is also elevated, strongly indicating biliary obstruction (LR+ 8.2). Meta-analyses on drug-induced liver injury show that cholestatic patterns have similar mortality to hepatocellular injury (9% vs 11%), challenging previous assumptions that hepatocellular injury is inherently more lethal.[24]

Dynamic Tests: Direct Assessment of Liver Function

Indocyanine Green (ICG) Clearance: This test quantifies the liver's ability to extract and excrete ICG, which is taken up via organic anion transporting polypeptides (OATP). With a high first-pass extraction rate (90%), a plasma disappearance rate below 12% per minute predicts safe liver resection in

92% of 3,200 cases. Retention exceeding 20% at 15 minutes indicates higher risk (OR 8.5). Compared to traditional scores like Child-Pugh, ICG clearance achieves about 28% higher area under the curve (AUC). Pediatric studies confirm that adult thresholds are applicable across a range of body sizes.[41]

Hepatobiliary Scintigraphy (99mTc-mebrofenin): This imaging modality assesses hepatocyte function by measuring uptake (via OATP1B1/1B3), storage, and excretion (via MRP2). A rate below 2.1%/min/m² signifies severe impairment. In surgical series, this technique reduced resection failure rates by 71% compared to static tests alone.[28-30]
Galactose Elimination Capacity (GEC): GEC evaluates the liver's capacity to metabolize galactose, which saturates UDP-glucuronyltransferase (Km 5 mmol/L). It correlates strongly with liver volume (r=0.78). Breath tests, such as 13C-methacetin demethylation, offer a non-invasive means to assess microsomal function, with an AUC of 0.82 for cirrhosis detection.[5,6]

Prognostic Models: Challenges in Integration
Child-Pugh vs MELD: Child-Pugh scoring, which includes subjective assessments like ascites and encephalopathy, shows moderate reproducibility (κ=0.55). MELD, based on objective lab measurements, performs better in transplant prioritization (c=0.83) but tends to underestimate early portal hypertension. Combining dynamic testing with volumetric analysis increases the prediction of safe resection to 94%, compared to 78% with scores alone.[28-31]

Disease-Specific Meta-Analyses:
LFT abnormalities such as AST elevations exceeding twice the normal are associated with increased ICU admission risk (OR 3.1), likely reflecting cytokine-mediated injury rather than direct viral effects. In NAFLD, ELF scores outperform traditional enzymes (AUROC 0.87 vs 0.72), with hyaluronic acid contributing substantially to diagnostic accuracy. Heart failure-related congestion elevates ALP and bilirubin independently of NAFLD, with a hazard ratio of 2.4 for decompensation.[15-18]

Emerging Patterns and Modifiable Factors
Interventions: Meta-analyses indicate that intermittent fasting reduces ALT by an average of 4.8 IU/L, likely by decreasing hepatic fat accumulation, without causing fibrosis progression—suggesting reversible enzyme leaks. Paradoxically, statins lower enzyme levels despite their cholesterol-lowering effects, probably through anti-inflammatory mechanisms.[5,6]

Serial Monitoring: In heart failure, peaks in bilirubin more than double the baseline improve the prediction of decompensation (AUC 0.79 versus 0.62). For chronic viral hepatitis, persistent ALT elevations above 200 IU/L predict hepatocellular carcinoma four times more accurately than absolute values alone.[5,6]

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