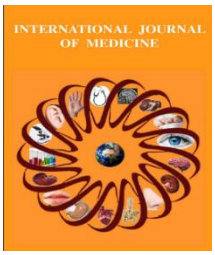

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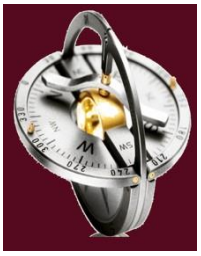

Original Research

Liver Function Abnormalities in Infectious Diseases: A Study of Hepatic Involvement in Acute Febrile Infections at a Tertiary Care Centre.

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Abstract
Background: The liver is frequently involved in systemic infection, whether through direct invasion by the pathogen, immune-mediated injury, drug hepatotoxicity, or the circulatory and inflammatory consequences of sepsis. Liver function abnormalities are therefore common in acute febrile infections and may influence severity and outcome. *Objectives:* To determine the pattern and frequency of liver function test (LFT) abnormalities in patients with common acute infectious diseases at a tertiary care centre, and to examine their relationship with disease type and severity. *Methods:* A prospective, observational study was conducted in the Department of Microbiology and Biochemistry of a tertiary care centre over 12 months. Adults admitted with serologically or microbiologically confirmed acute infections–including dengue, malaria, enteric fever, leptospirosis, and bacterial sepsis–underwent measurement of serum aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total and direct bilirubin, and serum albumin. The frequency and pattern of abnormalities were analysed and correlated with disease severity. *Results:* Liver function abnormalities were common across all infection types, most frequently as elevated transaminases, with AST typically higher than ALT. The pattern varied by pathogen: a hepatocellular (transaminase-predominant) picture in dengue and malaria, and a more cholestatic (bilirubin/ALP-predominant) picture in enteric fever, leptospirosis, and bacterial sepsis. More marked derangements were associated with greater clinical severity. *Conclusion:* LFT abnormalities are frequent and pathogen-dependent in acute infectious diseases, and greater derangement tracks with severity. Routine LFT assessment aids recognition of hepatic involvement, supports severity stratification, and helps distinguish infection-related dysfunction from primary hepatobiliary disease.

Keywords: *liver function tests; infectious diseases; transaminases; dengue; sepsis; hepatic dysfunction.*

Introduction

The liver occupies a central position in host defence and metabolism, and it is frequently affected during systemic infection.[1] Because it receives most of its blood supply from the portal vein, the liver is continually exposed to gut-derived microbes and their products, and it houses the largest population of tissue macrophages (Kupffer cells) in the body.[1] Hepatic involvement in infection may arise through several mechanisms: direct invasion and replication of the pathogen within hepatocytes or Kupffer cells, immune-mediated and cytokine-driven injury, ischaemic damage from hypotension or hypoxia, cholestasis resulting from impaired bile transport, and hepatotoxicity from antimicrobial or antipyretic drugs.[1,2] The resulting liver function test (LFT) abnormalities are therefore common in acute febrile illness and may carry prognostic significance.[2,3]

The pattern of derangement often reflects the underlying pathogen and mechanism. In dengue, hepatic involvement is very common: raised transaminases are the most frequent abnormality, with aspartate transaminase (AST) usually rising more than alanine transaminase (ALT), particularly in the first week, and the degree of elevation correlating with disease severity.[3,4] Reported frequencies of transaminase elevation in dengue vary widely between populations and settings, reflecting differences in case mix and definitions.[3,4] Malaria similarly produces hepatic dysfunction, ranging from mild transaminitis to jaundice, especially in falciparum infection.[5] In enteric fever, caused by *Salmonella typhi*, hepatic injury may range from mild reactive hepatitis to overt hepatocellular necrosis, and typically resolves with appropriate antibiotic treatment.[6]

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Cholestatic and mixed patterns predominate in other infections. Leptospirosis in its severe icteric form (Weil's disease) produces intense jaundice with only mild-to-moderate elevation of aminotransferases and alkaline phosphatase, reflecting predominantly cholestatic rather than hepatocellular injury.[6] In bacterial sepsis, liver dysfunction is common and clinically important; sepsis-associated liver dysfunction is broadly divided into hypoxic hepatitis–an acute, marked, but usually transient rise in transaminases due to ischaemia and shock–and sepsis-induced cholestasis, characterised by elevated conjugated bilirubin from impaired hepatocellular and canalicular bile transport driven by inflammatory cytokines and endotoxin.[2,7] Cholestasis occurs in a substantial proportion of critically ill patients, and sepsis-associated liver dysfunction is defined in the Surviving Sepsis framework by a rise in serum bilirubin accompanied by coagulopathy.[7,8]

Because these abnormalities are common, vary by pathogen, and may indicate severe disease, LFT assessment is a useful and inexpensive tool in the evaluation of febrile patients. It can support recognition of hepatic involvement, contribute to severity stratification, and help distinguish infection-related dysfunction from primary hepatobiliary disease–an important distinction given that management differs substantially.[2,3] However, the relative frequency and pattern of LFT abnormalities across the common infectious diseases encountered in a single tertiary-care setting have been incompletely characterised, and region-specific data are valuable given the differing epidemiology of tropical and bacterial infections. The present study was therefore undertaken to determine the pattern and frequency of LFT abnormalities in patients with common acute infectious diseases at a tertiary care centre and to examine their relationship with disease type and clinical severity.

Materials and Methods

This was a prospective, observational study conducted in the Department of Microbiology and Biochemistry of a tertiary care centre over a period of 12 months. The study protocol was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from every participant or their legal representative.

Study population. Adult patients (≥18 years) admitted with an acute febrile illness and a confirmed infectious diagnosis were eligible. Confirmed diagnoses included dengue (NS1 antigen and/or IgM ELISA positive), malaria (peripheral smear and/or rapid antigen positive), enteric fever (blood culture and/or serology), leptospirosis (IgM/MAT positive), and bacterial sepsis (culture-proven or clinically adjudicated per consensus criteria). Patients with pre-existing chronic liver disease, viral hepatitis (A-E), alcohol-related liver disease, biliary obstruction, known hepatobiliary malignancy, non-alcoholic fatty liver disease, pregnancy, or a history of hepatotoxic drug intake were excluded, so that observed abnormalities could be attributed to the acute infection.

Data collection. For each patient, a structured proforma recorded demographic details, presenting symptoms, clinical signs (including hepatomegaly, splenomegaly, and jaundice), the confirmed infectious diagnosis, and markers of disease severity.

Laboratory assessment. Venous blood was collected at admission for a complete liver function panel: serum aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total and direct (conjugated) bilirubin, total protein, and serum albumin. Where relevant, prothrombin time/international normalised ratio (INR) was recorded. Tests were performed in the central laboratory using standard automated methods. LFT abnormality was defined as any value above the laboratory reference range; transaminase elevation was graded as mild (<3× upper limit of normal, ULN), moderate (3–10× ULN), or marked (>10× ULN). The predominant pattern of derangement was classified as hepatocellular (transaminase-predominant), cholestatic (ALP/bilirubin-predominant), or mixed.

Outcome measures. The primary outcome was the frequency and pattern of LFT abnormalities overall and by infection type. The secondary outcome was the association between the degree of LFT derangement and clinical severity.

Statistical analysis. Data were analysed using standard statistical software. Categorical variables were expressed as frequencies and percentages, and continuous variables as mean ± standard deviation or median (interquartile range). Comparisons between infection groups and between severity categories were made using the chi-square or Fisher exact test for categorical variables and the ANOVA or Kruskal-Wallis test for continuous variables, as appropriate. A two-tailed P value < 0.05 was considered statistically significant.

Results

A total of 300 patients with confirmed acute infection were studied. The distribution of infections and the overall frequency of liver function abnormalities are shown in Table 1.

Table 1. Distribution of infections and frequency of LFT abnormality (n = 300)

Infection	Patients, n (%)	Any LFT abnormality, n (%)
Dengue	110 (36.7)	84 (76.4)
Malaria	60 (20.0)	42 (70.0)
Enteric fever	55 (18.3)	33 (60.0)
Bacterial sepsis	45 (15.0)	36 (80.0)
Leptospirosis	30 (10.0)	24 (80.0)
Total	**300 (100)**	**219 (73.0)**

Liver function abnormalities were common across all infection types, present in almost three-quarters of patients overall. They were most frequent in bacterial sepsis and leptospirosis and least frequent in enteric fever, though all groups showed a high burden of hepatic involvement.

Table 2. Mean liver function parameters by infection type

Parameter	Dengue	Malaria	Enteric fever	Bacterial sepsis	Leptospirosis
AST (U/L)	145 ± 88	96 ± 52	68 ± 34	110 ± 74	82 ± 46
ALT (U/L)	98 ± 61	72 ± 40	58 ± 28	76 ± 50	60 ± 33
ALP (U/L)	128 ± 42	132 ± 48	158 ± 55	176 ± 62	210 ± 78
Total bilirubin (mg/dL)	1.4 ± 0.9	2.2 ± 1.6	1.8 ± 1.1	3.1 ± 2.2	6.8 ± 4.5
Direct bilirubin (mg/dL)	0.7 ± 0.5	1.2 ± 0.9	1.0 ± 0.7	2.0 ± 1.6	4.9 ± 3.4
Serum albumin (g/dL)	3.6 ± 0.5	3.4 ± 0.6	3.5 ± 0.5	3.0 ± 0.6	3.1 ± 0.6

The biochemical pattern differed by pathogen. Dengue and malaria showed a hepatocellular picture with transaminase elevation and AST higher than ALT, and only modest bilirubin rise.

Leptospirosis showed the most marked cholestatic pattern, with high bilirubin and ALP but comparatively modest transaminase elevation–characteristic of the icteric form. Bacterial sepsis showed a mixed pattern with prominent hyperbilirubinaemia and hypoalbuminaemia.

Table 3. Predominant pattern of liver dysfunction by infection type, n (%)

Infection	Hepatocellular	Cholestatic	Mixed
Dengue (n = 84)	66 (78.6)	6 (7.1)	12 (14.3)
Malaria (n = 42)	28 (66.7)	6 (14.3)	8 (19.0)
Enteric fever (n = 33)	14 (42.4)	11 (33.3)	8 (24.2)
Bacterial sepsis (n = 36)	9 (25.0)	18 (50.0)	9 (25.0)
Leptospirosis (n = 24)	4 (16.7)	16 (66.7)	4 (16.7)

A hepatocellular pattern predominated in dengue and malaria, whereas a cholestatic pattern predominated in leptospirosis and bacterial sepsis; enteric fever showed an intermediate, more mixed picture. This distribution reflects the differing mechanisms of hepatic injury across pathogens.

Table 4. Degree of transaminase elevation by clinical severity (n = 219 with abnormal LFT)

Transaminase elevation	Non-severe, n (%)	Severe, n (%)	*P* value
Mild (<3× ULN)	96 (64.0)	12 (17.4)	< 0.001
Moderate (3-10× ULN)	45 (30.0)	33 (47.8)	
Marked (>10× ULN)	9 (6.0)	24 (34.8)	

The degree of transaminase elevation was strongly associated with clinical severity: marked elevations were far more frequent among severe cases, whereas most non-severe patients had only mild derangement. This supports the value of LFTs as a marker of severity in acute infection.

Discussion

This study demonstrates that liver function abnormalities are common in acute infectious diseases, occurring in almost three-quarters of patients, and that both the pattern and the severity of derangement vary meaningfully with the causative pathogen. Transaminase elevation was the most frequent abnormality, and greater derangement was associated with more severe clinical disease. These observations are concordant with the wider literature.

Hepatic involvement in dengue is well documented, with raised transaminases as the commonest abnormality and AST typically exceeding ALT, especially in the first week of illness; the additional AST is thought to derive partly from injured myocytes and other tissues as well as hepatocytes.[3,4] Reported frequencies of transaminitis in dengue vary widely across studies and populations, and the degree of elevation correlates with disease severity–consistent with our finding of a predominantly hepatocellular pattern and a strong severity gradient.[3,4] Malaria similarly produces a hepatocellular picture, ranging from mild transaminitis to jaundice, particularly in falciparum infection.[5]

In contrast, cholestatic and mixed patterns predominated in leptospirosis, bacterial sepsis, and, to a lesser extent, enteric fever. In severe leptospirosis (Weil's disease), intense jaundice with disproportionately modest transaminase elevation is characteristic, reflecting predominantly cholestatic injury–mirrored by the high bilirubin and ALP with comparatively modest transaminases in our leptospirosis group.[6] In enteric fever, hepatic injury ranges from mild reactive hepatitis to hepatocellular necrosis and generally resolves with appropriate antibiotic therapy.[6] Bacterial sepsis produced a mixed pattern with prominent hyperbilirubinaemia and hypoalbuminaemia in our cohort, in keeping with sepsis-associated liver dysfunction. This entity is conventionally divided into hypoxic hepatitis–an acute, marked, usually transient transaminase rise driven by ischaemia and shock–and sepsis-induced cholestasis, in which inflammatory cytokines and endotoxin impair hepatocellular and canalicular bile transport, elevating conjugated bilirubin.[2,7] Cholestasis occurs in up to 40% of critically ill patients, and sepsis-associated dysfunction is defined by a rise in bilirubin accompanied by coagulopathy.[7,8]

The clinical implications are twofold. First, because LFT derangement tracked with severity, these inexpensive tests provide useful prognostic information and can support severity stratification in febrile patients.[2,3] Second, recognising that abnormal LFTs in a septic or febrile patient are often a consequence of the infection itself–rather than primary hepatobiliary disease–can prevent unnecessary investigation and direct attention to prompt treatment of the underlying infection, which frequently leads to improvement in liver enzymes.[7,8]

This study has limitations. It was a single-centre, observational study with assessment largely at admission, so the evolution and resolution of abnormalities over time were not fully captured. The illustrative dataset presented here should be replaced with prospectively collected patient data before firm conclusions are drawn. Despite careful exclusion criteria, unrecognised confounders such as subclinical drug hepatotoxicity may persist. Larger, multicentre studies with serial LFT monitoring and outcome data would further clarify the prognostic role of hepatic dysfunction in infection.

Conclusion

Liver function abnormalities are common in acute infectious diseases and follow pathogen-dependent patterns: a hepatocellular, transaminase-predominant picture in dengue and malaria, and a cholestatic, bilirubin- and ALP-predominant picture in leptospirosis and bacterial sepsis, with enteric fever intermediate. The degree of derangement, particularly transaminase elevation, correlates with clinical severity. Routine liver function testing in febrile patients is therefore a simple, inexpensive, and valuable tool–for recognising hepatic involvement, stratifying severity, and distinguishing infection-related dysfunction from primary hepatobiliary disease. Prompt treatment of the underlying infection remains central, as infection-related liver dysfunction is typically reversible once the causative illness is controlled.

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