Journal of Natural and Applied Sciences Research
jnasr@iuokada.edu.ng Available online at www/jnasr.iuokada.edu.ng.

JNASR 1(2): Ibezim *et al*., (2025) pp 1-9.

Gamma-Glutamyl Transferase and Alkaline Phosphatase Profiles as Indicators of Cholestatic and Toxic Liver Injury in Non-Viral Hepatitis Patients in Rural Nigeria

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ABSTRACT
Non-viral causes of liver dysfunction, including alcohol consumption, herbal toxicity, and aflatoxin exposure, are increasingly prevalent yet remain underdiagnosed in rural Nigeria, where diagnostic facilities are limited. Gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) are key hepatic enzymes that reflect cholestatic and toxin-induced injury, serving as valuable biochemical tools for assessing non-viral hepatic disorders. This retrospective cross-sectional study examined 100 adult patients (≥18 years) at Igbinedion University Teaching Hospital, Okada, who presented with abnormal liver function tests but tested negative for viral hepatitides. Serum GGT and ALP activities were measured using International Federation of Clinical Chemistry (IFCC) enzymatic colorimetric methods, and data were analysed with SPSS version 26 using Chi-square and Kendall's tau-b correlation tests, with a significance threshold of $p < 0.05$. The findings revealed that all participants (100%) had elevated GGT levels (>48 U/L), while 71% showed increased ALP activity (>147 U/L). Herbal toxicity (20%) and alcoholic hepatitis (20%) were the predominant aetiologies associated with enzyme elevation, followed by drug-induced liver injury (15%) and aflatoxin exposure (15%). A statistically significant association was observed between ALP levels and the identified causes of hepatic injury ($\chi^2 = 40.34$; $p < 0.05$). These results demonstrate that the combined evaluation of GGT and ALP provides a sensitive, practical, and cost-effective method for detecting early cholestatic and toxin-induced hepatic injury, particularly in resource-limited rural settings where non-viral liver diseases are often underdiagnosed.

Keywords: Non-viral hepatitis, Gamma-glutamyl transferase (GGT), Alkaline phosphatase (ALP); Cholestatic liver injury, Herbal hepatotoxicity, Alcoholic hepatitis.

1. INTRODUCTION

Liver diseases remain a major global health challenge, contributing significantly to morbidity and mortality worldwide. According to the World Health Organization (*WHO*, 2023), liver-related illnesses account for approximately two million deaths annually, with cirrhosis and hepatic failure ranking among the leading causes. While viral hepatitis continues to be a major contributor to liver pathology, non-viral factors are increasingly recognised as substantial causes of hepatic dysfunction, particularly in developing regions (Ibezim *et al*., 2025; Asrani *et al.*, 2019). These non-viral causes include chronic alcohol consumption, exposure to hepatotoxic herbal preparations, aflatoxin ingestion,

metabolic disorders, and drug-induced liver injury (Chalasani *et al.*, 2015; Ogun & Adetiloye, 2020).

In sub-Saharan Africa, including Nigeria, non-viral liver diseases are often underdiagnosed due to poor access to diagnostic facilities, unregulated traditional medicine use, and limited public health awareness (Afolabi *et al.*, 2012). Herbal concoctions and locally prepared medicinal mixtures are commonly used as remedies for various ailments, yet many contain hepatotoxic alkaloids, heavy metals, and aflatoxin contaminants that contribute to hepatic inflammation and bile duct obstruction (Teschke & Eickhoff, 2015; Onyije *et al.*, 2021). Similarly, alcohol misuse remains a major risk factor, causing oxidative stress, mitochondrial dysfunction, and enzyme induction leading to hepatocellular and cholestatic injury (Seitz & Stickel, 2010).

Gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) are crucial biochemical markers in assessing hepatic function and bile flow. GGT, a microsomal enzyme found predominantly in the hepatocytes and biliary epithelial cells, reflects oxidative stress, bile duct damage, and enzyme induction by hepatotoxins (Whitfield, 2001; Lee *et al.*, 2020). Elevated GGT levels have been linked to both alcohol-induced hepatotoxicity and non-alcoholic liver injury, serving as a sensitive indicator of hepatic stress even before clinical symptoms manifest (Targher *et al.*, 2017). ALP, on the other hand, is primarily associated with the canalicular and sinusoidal membranes of the liver; its elevation indicates cholestasis, biliary obstruction, or infiltrative hepatic disease (Giannini *et al.*, 2005; Friedman *et al.*, 2018).

The combined assessment of GGT and ALP provides valuable diagnostic insight into differentiating cholestatic injury from hepatocellular damage. In rural Nigerian settings, where advanced imaging and histopathological assessments are rarely accessible, enzyme-based diagnostics offer a cost-effective and reliable approach to early detection of hepatic impairment (Eze *et al.*, 2020). Therefore, this study evaluates the prevalence and diagnostic patterns of GGT and ALP among non-viral hepatitis patients at Igbinedion University Teaching Hospital (IUTH), Okada, with the aim of identifying their clinical significance as markers of cholestatic and toxin-induced hepatic injury.

2. METHODS

2.1 Study Design

This retrospective cross-sectional study was conducted at Igbinedion University Teaching Hospital (IUTH), Okada, Edo State, Nigeria, between January 2023 and March 2025. The study aimed to assess liver enzyme alterations among adults with non-viral liver dysfunction.

Study Population

A total of 100 adult patients (≥18 years) with abnormal liver enzyme profiles but negative viral serology for hepatitis A, B, C, D, and E were included in the study. All participants had complete clinical and laboratory records relevant to liver function assessment.

Sample Size Determination

The minimum sample size was determined using the Cochran formula (1977) for cross-sectional studies:

$n = Z^2 \times p(1–p) / d^2$

- n = desired sample size
- Z = 1.96 (standard normal deviation for 95% confidence level)
- p = estimated prevalence of non-viral liver dysfunction (assumed at 0.5 for maximum variability)
- d = margin of error (0.1)

Substituting these values:

$n = (1.96^2 \times 0.5\ (1 – 0.5)) / 0.1^2$

$n = (3.8416 \times 0.25) / 0.01$

$n = 0.9604 / 0.01$

$n = 96.04$

To compensate for incomplete data and possible exclusions, the sample size was adjusted to 100 participants.

Inclusion criteria

The study included adults aged 18 years and above with elevated liver enzymes (GGT and/or ALP) and negative viral serology for hepatitis A-E.

Exclusion criteria

The study excluded individuals younger than 18 years, patients with confirmed viral hepatitis, and those with incomplete laboratory or clinical data.

2.2 Data Collection

Demographic information, clinical features, potential risk factors (including alcohol consumption and medication history), and final diagnoses were retrieved from hospital records using a standardised data extraction form. For analytical clarity, diagnoses were systematically grouped into clinically meaningful categories such as alcoholic hepatitis, drug-induced liver injury (DILI), autoimmune hepatitis, aflatoxin-related liver damage, parasitic infection, protein-energy deficiency, and herbal toxicity. Diagnostic classification was collaboratively performed by the attending Medical Officer and subsequently reviewed by a Chief Consultant, in partnership with the Department of Biochemistry, to ensure uniformity and accuracy in diagnostic categorisation.

2.3 Parameters Measured

The key biochemical parameters assessed were gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP). These enzymes were analysed to evaluate patterns of liver dysfunction and possible cholestatic or hepatocellular injury.

2.4 Biochemical Analyses

Serum samples were obtained following standard venipuncture procedures and analysed within two hours of collection to minimise enzymatic degradation. Biochemical assays for gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) were performed using spectrophotometric methods in accordance with the recommendations of the International Federation of Clinical Chemistry (IFCC, 2002).

2.4.1 Gamma-Glutamyl Transferase (GGT) Assay

Serum GGT activity was determined using a kinetic colorimetric method based on the procedure described by Szasz (1969). In this assay, GGT catalyses the transfer of the γ-glutamyl group from L-γ-glutamyl-p-nitroanilide to glycyl-glycine, yielding p-nitroaniline, which is measured at 405 nm. The rate of increase in absorbance is directly proportional to GGT activity in the sample, and results were expressed in U/L at 37 °C (Szasz, 1969).

2.4.2 Alkaline Phosphatase (ALP) Assay

ALP activity was measured using a kinetic spectrophotometric method in which the enzyme hydrolyses p-nitrophenyl phosphate (pNPP) to p-nitrophenol (pNP) and inorganic phosphate under alkaline conditions, following the IFCC-recommended procedure (Tietz *et al.*, 2012; IFCC, 2002). The formation of yellow-coloured p-nitrophenol was monitored at 405 nm, and enzyme activity was reported in units per litre (U/L) at 37 °C.

All analyses were performed using an automated chemistry analyser (e.g., Mindray BS-240, Shenzhen, China). Calibration was performed daily with manufacturer-supplied standards and controls to ensure analytical accuracy and precision. Quality control sera were included with each batch of assays in accordance with standard laboratory quality assurance protocols (Tietz *et al.*, 2012).

2.5 Statistical Analyses:

Data were analysed using the Statistical Package for the Social Sciences (SPSS), version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were generated to summarise participant characteristics, with categorical variables (e.g., sex, age group, etiological classification) presented as frequencies and percentages. Continuous variables were grouped into categories where necessary to facilitate comparative analyses across study subgroups.

Associations between categorical variables were assessed using Pearson's Chi-square (χ^2) test, while the strength and direction of correlations between biochemical parameters (GGT and ALP) were determined using Kendall's tau-b correlation coefficient. These tests were chosen to evaluate both statistical association and ordinal correlation among non-parametric data (Field, 2013).

All statistical tests were conducted at a 95% confidence level, and results were considered statistically significant at a p-value < 0.05 (Pallant, 2020).

2.6 Ethical Consideration.

Ethical clearance for this study was granted by the Health Research Ethics Committee (HREC) of

Igbinedion University Teaching Hospital (IUTH), Okada, Edo State, Nigeria, under protocol number IUTH/R.24/VOL.I/156. All patient information was handled with strict confidentiality, and identifiers were removed before analysis. The study was conducted in full compliance with the ethical principles of the Declaration of Helsinki governing research involving human participants (World Medical Association, 2013).

3. RESULTS

3.1 Liver Enzymes Patterns and Aetiological Distribution

Among the 100 participants, all (100%) exhibited elevated GGT levels (>48 U/L), while 71% showed elevated ALP levels (>147 U/L). Regarding aetiological distribution, herbal toxicity and alcoholic hepatitis each accounted for the largest proportion of cases (20%, respectively). This was followed by drug-induced liver injury (DILI) and aflatoxin-related hepatic damage, contributing 15% each. Autoimmune hepatitis, parasitic infection and protein-energy deficiency represented smaller but notable fractions of the study population (10% each). These findings highlight the predominance of toxin-related liver injury as a major contributor to non-viral hepatic dysfunction within the studied population.

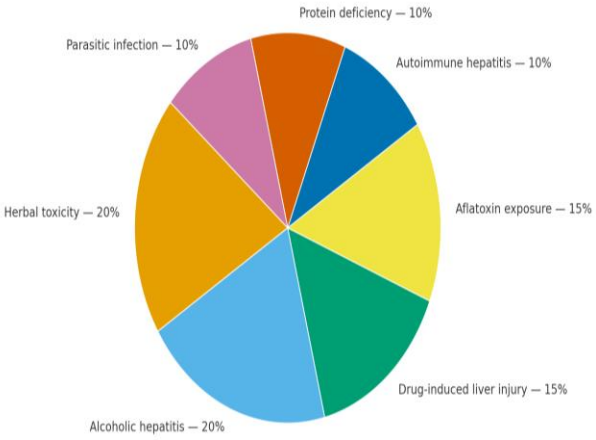

Figure 1: Distribution of Aetiological Categories with Elevated GGT(>48U/L) and ALP (>147U/L)

3.2 Association between Liver Enzymes (GGT and ALP) and Aetiological Categories

The Chi-square (χ^2) analysis demonstrated a statistically significant relationship between ALP levels and the various aetiological categories assessed ($\chi^2 = 40.34$, $p < 0.05$). Among participants with elevated ALP, the most frequently associated conditions were herbal toxicity (n = 20), alcoholic hepatitis (n = 15), and drug-induced liver injury (n = 13). . This finding indicates that the distribution of elevated ALP activity differed markedly across the identified causes of hepatic dysfunction. Furthermore, correlation analysis using Kendall's tau-b revealed a moderate positive association between GGT elevation and toxin-related aetiologies ($\tau b = 0.331$, $p = 0.003$). These results collectively suggest a consistent pattern of enzyme elevation that aligns with the underlying biochemical disturbances characteristic of the respective liver injury categories.

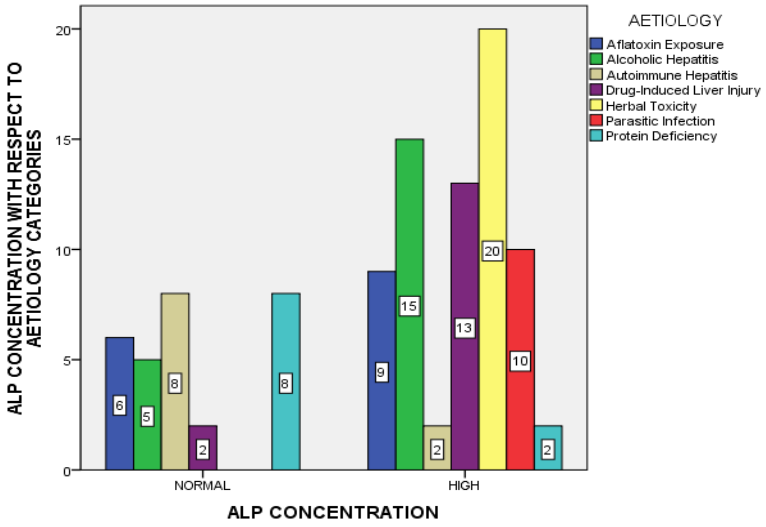

Figure 2: Relationship between ALP and Aetiologies among Patients with Non-Viral Hepatitis
Normal ALP= 44-147 IU/L, High ALP= >147 IU/L
($\chi^2 = 40.343$, $p < 0.05$).

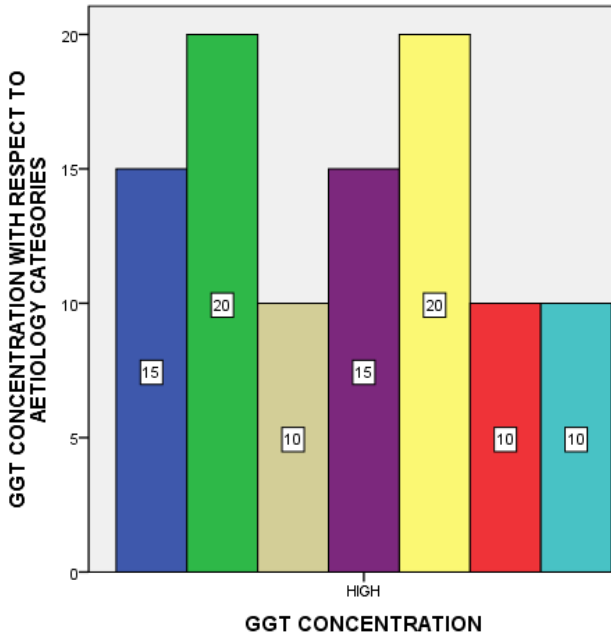

Figure 3: Relationship between GGT and Aetiologies among Patients with Non-Viral Hepatitis
Normal GGT= 9 – 48 U/L, High GGT= >48 U/L
($\chi^2 = 89.855$, $P < 0.05$)

4. DISCUSSION

4.1 Liver Enzymes Patterns and Aetiological Distribution

GGT was elevated above 48 U/L in all 100 participants. This uniform elevation reflects the dominant aetiological profile of our sample, in which conditions associated with hepatic enzyme induction, such as metabolic syndrome, alcohol use, chronic medication exposure, and herbal remedy consumption, were highly prevalent. These aetiologies are well-established triggers of microsomal enzyme induction, explaining why GGT was universally elevated, even in participants without clinically overt liver disease. The sensitivity of GGT to subclinical hepatic stress has been consistently reported in the literature. For instance, a large retrospective study among non-obese Chinese adults demonstrated a strong positive association between higher GGT quartiles and incident non-alcoholic fatty liver disease (NAFLD) (Liu *et al.*, 2021). Similarly, elevated GGT independently predicted type 2 diabetes prevalence in Bangladeshi adults (Uddin *et al.*, 2020). These external comparisons underscore that GGT elevation is not only a marker of liver injury but also reflects broader metabolic and hepatotoxic exposures, paralleling the aetiological landscape observed in our study population.

ALP levels exceeding 147 U/L were present in 71% of participants, indicating a substantial burden of cholestatic-type injury within the cohort. This aligns with the aetiological distribution, as a sizeable proportion of participants had risk factors known to provoke cholestasis, including suspected herb-induced liver injury, metabolic dysfunction, and biliary-related symptoms. ALP, which is highly expressed on canalicular and biliary epithelial surfaces, rises in response to bile duct obstruction, cholestasis, or infiltrative hepatic processes (Levitt *et al.*, 2022; Pollock *et al.*, 2017). Accumulating bile acids stimulate ALP production, and when canalicular transport is overwhelmed, ALP spills into the circulation (Shroff *et al.*, 2020). In many hepatobiliary disorders, ALP elevations often exceed those of aminotransferases, reinforcing its specificity for cholestatic injury patterns (Kamath *et al.*, 1996).

In our setting, the widespread use of traditional herbal preparations is well-documented, and a notable proportion of participants reported recent herbal consumption. Given the established hepatotoxic potential of several phytochemicals, particularly their tendency to produce cholestatic enzyme patterns—herbal exposure represents a plausible contributor to the ALP elevations observed (Ballotin *et al.*, 2021; Amadi *et al.*, 2018; Stickel *et al.*, 2005). Thus, the ALP and GGT patterns observed in this cohort closely mirror the aetiological distribution and exposures characteristic of our population.

4.2 Association between Liver Enzymes (GGT and ALP) and Aetiological Categories

GGT, primarily localised in hepatocytes and biliary epithelial cells, is a sensitive biomarker of hepatobiliary perturbation. While its elevation commonly reflects direct cholestatic or hepatocellular injury, GGT is also inducible by chronic alcohol use, various medications, and environmental hepatotoxins (Lonardo *et al.,* 2022; Thakur *et al.*, 2024). In this cohort, the universal elevation of GGT aligns with its role as a broadly responsive indicator of hepatic stress across diverse

injury modalities. The marked increases in GGT observed in participants with alcoholic hepatitis and herbal toxicity are consistent with known pathophysiological mechanisms. Chronic alcohol ingestion induces hepatic microsomal enzyme systems and fosters oxidative stress, both of which upregulate GGT expression (Thakur *et al.*, 2024). Likewise, hepatotoxic compounds in traditional herbal preparations may inflict direct or indirect injury on hepatocytes and biliary structures, leading to enhanced GGT release (Biomarkers of Hepatic Toxicity: An Overview, 2024).

Notably, subsets of patients exposed to aflatoxin and those with drug-induced liver injury (DILI) also demonstrated substantial GGT elevation. Aflatoxin exposure is known to inflict extensive hepatocellular damage and stimulate bile duct proliferation, both of which can contribute to increased GGT activity (Wild & Gong, 2010). Similarly, certain medications, especially those processed extensively in the liver, can cause hepatocellular stress or idiosyncratic reactions, resulting in elevated GGT levels (Chalasani e*t al*., 2015). Interestingly, protein deficiency (n = 10) was also associated with elevated GGT in this study population. Although malnutrition is typically linked to reduced synthetic capacity, there is emerging evidence that hepatic stress and adaptive enzyme induction may occur even in nutritionally compromised individuals (Nishioka *et al*., 2018). Indeed, animal studies have demonstrated that protein restriction can alter GGT activity, possibly via oxidative stress pathways or compensatory upregulation of detoxification enzymes (de Oliveira *et al*., 2000).

Although all participants demonstrated elevated GGT levels, categorical stratification based on the degree of elevation permitted statistical comparison across etiological groups. The Chi-square test revealed a statistically significant association between GGT levels and the underlying causes of liver dysfunction, suggesting that the magnitude of GGT elevation differed meaningfully among the various aetiologies. Furthermore, Kendall's tau-b correlation analysis indicated a moderate positive association between GGT concentration and toxin-related liver injury patterns, underscoring GGT's responsiveness to hepatocellular and cholestatic stress. These results reinforce the enzyme's diagnostic sensitivity and its potential value in distinguishing toxin-mediated from metabolic or autoimmune hepatic dysfunctions, particularly when interpreted alongside complementary biochemical markers (Thakur *et al*., 2024; Lonardo *et al*., 2022).

Among participants exhibiting elevated ALP, the predominant etiologies identified were herbal-induced liver injury (HILI) (n = 20), alcoholic hepatitis (n = 15), and drug-induced liver injury (DILI) (n = 13). Conversely, individuals with normal ALP levels were more frequently associated with protein deficiency and autoimmune hepatitis (n = 8 each). Statistical analysis confirmed the significance of these associations ($p < 0.05$), highlighting the clinical utility of ALP measurements in differentiating between cholestatic and hepatocellular patterns of liver injury. Herbal remedies, often utilised in low- and middle-income countries without stringent regulatory oversight, have been implicated in hepatotoxicity. These substances can induce intrahepatic cholestasis and bile duct injury, leading to elevated ALP levels. Recent studies have highlighted the hepatotoxic potential of various herbal supplements, emphasising the need for caution and regulatory measures (Alves *et al*., 2022; Navarro, 2016).

Alcoholic hepatitis is characterised by hepatocellular injury and cholestasis, with ALP levels typically elevated to a moderate extent. While ALP elevation is usually mild, levels exceeding 500 U/L may indicate concurrent biliary obstruction or infiltrative processes (Axley *et al*., 2017; Khatiwada *et al*., 2020). DILI encompasses a spectrum of liver injuries, including hepatocellular, cholestatic, and mixed patterns. Cholestatic DILI is associated with significant elevations in ALP levels. The variability in ALP elevations among DILI cases necessitates comprehensive evaluation, including assessment of gamma-glutamyl transferase (GGT) levels to ascertain the hepatic origin of ALP elevation (Devarbhavi, 2012; EASL, 2019). In contrast, conditions such as protein deficiency and autoimmune hepatitis often present with normal ALP levels. Protein deficiency may result in reduced synthesis of hepatic enzymes, including ALP, leading to normal or low serum ALP concentrations (Verywell Health, 2025). Autoimmune hepatitis typically manifests with elevated

transaminases and normal ALP levels, particularly in its early stages (Cleveland Clinic, 2024). The findings of this study corroborate the established role of ALP as a sensitive marker for cholestatic liver injury. However, the elevation of ALP should be interpreted in conjunction with other liver function tests and clinical parameters to accurately delineate the underlying aetiology. Further research is warranted to explore the pathophysiological mechanisms linking ALP elevation to specific hepatic disorders and to refine diagnostic algorithms incorporating ALP measurements.

5. CONCLUSION

GGT and ALP are well-established biochemical indicators of cholestatic and toxin-related hepatic stress. In this study, both enzymes were frequently elevated among individuals with non-viral hepatitis, reflecting the substantial burden of hepatotoxic exposures in this low-resource setting. While this study did not assess diagnostic performance or predictive accuracy, the observed enzyme patterns offer preliminary insight into the spectrum of liver dysfunction encountered in the population. From a public health perspective, incorporating GGT and ALP into routine liver function panels at primary and secondary healthcare facilities may support earlier clinical recognition of hepatocellular stress, especially in environments where alcohol use, herbal remedy consumption, and environmental hepatotoxins are common. Targeted community education on the risks of unregulated herbal preparations, excessive alcohol intake, and aflatoxin exposure remains important for prevention. Strengthening laboratory capacity and implementing clearer regulatory policies around hepatotoxic exposures will be essential to reducing the burden of preventable liver injury in rural communities.

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