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Development of a Predictive Model for Hepatitis B Virus (HBV) Status Using Gender and Serum Biomarkers

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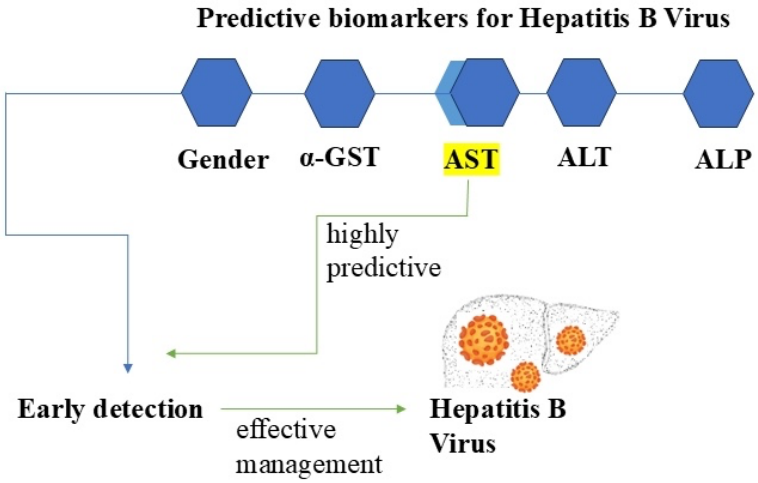
Graphical Abstract



Abbreviations: alpha glutathione S-transferase (α–GST), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP).

Abstract

Early screening for the Hepatitis B Virus (HBV) is crucial for effective management and treatment, especially in resource-limited areas like Enugu State, Nigeria. This study aims to develop and validate a predictive model for HBV status. By integrating several factors, this research seeks to improve diagnostic accuracy and contribute to more effective HBV management, particularly in resource-limited settings. The study is focused on the following gender and serum biomarkers: alpha glutathione S-transferase (α-GST), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) among patients at Enugu State University Teaching Hospital. Binary logistic regression was employed to analyze the predictive power of these variables. The results indicate that AST is a statistically significant predictor of HBV status. In contrast, gender, alpha GST, ALP, and ALT were not statistically significant predictors in the model.

Keywords Hepatitis B Virus (HBV), Predictive Model, Gender and Serum Biomarkers, Binary Logistic Regression

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Rationale, Purpose, and Limitations

This study was motivated by the need for early, cost-effective screening tools for Hepatitis B Virus (HBV) in resource-limited settings like Enugu State, Nigeria, where access to advanced diagnostics is limited. The purpose was to develop a predictive model using gender and common serum biomarkers to identify HBV status, potentially guiding timely clinical intervention. The findings may help improve HBV management in similar low-resource environments. However, the study's limitations include focusing on a single center, limited sample diversity, and excluding other potentially relevant biomarkers.

Introduction

Hepatitis B Virus (HBV) is a significant global health concern, causing chronic liver infection that can lead to severe complications such as cirrhosis and liver cancer. As of 2022, an estimated 257 million people worldwide are living with chronic HBV infection, with high prevalence rates in sub-Saharan Africa and East Asia[1]. In Nigeria, HBV is a significant public health issue, with an estimated prevalence rate of 13.6%, indicating one of the highest burdens of chronic HBV infection globally[2].

Transmission primarily occurs through contact with infectious blood and body fluids, perinatally from mother to child during childbirth, and through unsafe medical practices and sexual contact[3]. The impact of HBV in Nigeria is profound, contributing to high rates of chronic liver disease, including cirrhosis and hepatocellular carcinoma[4]. The Nigerian healthcare system faces numerous challenges, including limited access to HBV screening, vaccination, and treatment services. Despite the availability of HBV vaccines and antiviral therapies, coverage remains insufficient, particularly in rural and underserved areas[5].

Enugu State, located in southeastern Nigeria, reflects many of the broader challenges faced by the country in managing HBV. Studies indicate an infection rate ranging from 7% to 11% in the state[6]. With a population of approximately 3.2 million people, HBV poses a significant public health challenge in the state. The diagnosis and management of HBV in Enugu State are hindered by a lack of comprehensive screening programs, limited access to diagnostic facilities, and the high cost of serological tests and liver function assessments[7]. The reliance on invasive diagnostic methods, such as liver biopsies, further exacerbates the problem, making timely and accurate diagnosis difficult[8]. Public awareness campaigns and vaccination programs have been established to address HBV in the state; however, these initiatives face challenges related to resource constraints and infrastructural limitations[9]. There is a pressing need for more accessible, non-invasive diagnostic methods to improve early detection and management of HBV.

In an ideal scenario, HBV infection would be accurately diagnosed and managed using reliable and accessible methods. Healthcare professionals would have predictive models that enable efficient determination of HBV status using a combination of easily measurable biomarkers and patient demographics, such as gender[10]. This would facilitate early detection, timely treatment, and improved patient outcomes. Currently, HBV detection and management in Nigeria remain suboptimal. Diagnosis often relies on resource-intensive tests, such as HBV DNA quantification or liver biopsies, which are not always available or affordable[11]. Moreover, there is limited use of predictive models that incorporate both demographic factors (e.g., gender) and routine laboratory tests (e.g., serum biomarkers) for identifying HBV status in patients[12]. While research acknowledges gender and biomarker variations in HBV progression, no specific predictive model has been developed to integrate these factors in this setting[13]. This gap leaves healthcare providers with less efficient methods for early diagnosis and personalized treatment plans.

Gender differences have been implicated in various infectious diseases, including HBV, due to biological, immunological, and behavioral factors. Studies suggest that males are more likely to develop chronic HBV infection, cirrhosis, and hepatocellular carcinoma than females, potentially due to hormonal influences, genetic predisposition, and differences in immune response[14]. Androgens have been associated with HBV replication and disease progression, whereas estrogens appear to confer some protective effects against HBV-related liver damage[15]. Additionally, social and behavioral factors such as healthcare-seeking behavior and exposure risks may contribute to gender-based differences in HBV prevalence and disease

course[16]. Despite this, gender has often been considered a non-predictive factor in HBV status assessments, and its inclusion in predictive models requires further validation[17].

The term "HBV status" in this study refers to the presence or absence of HBV infection, as determined by serological markers and liver function tests. It does not explicitly assess the transition from acute to chronic infection, cirrhosis to hepatocellular carcinoma, or the extent of liver damage. However, understanding these disease progression stages is essential, as HBV infection can exist in various clinical states, from asymptomatic carriers to severe liver pathology[18]. By predicting HBV status, this study aims to contribute to earlier detection of infection, thereby enabling prompt intervention and monitoring to prevent progression to severe liver disease[19].

This study incorporates four key serum biomarkers - Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), and Total Bilirubin (TB), alongside gender in predicting HBV status. These biomarkers were selected based on their roles in liver function and potential relevance in HBV-related liver pathology. AST and ALT are widely recognized indicators of hepatocellular injury and have been frequently used in HBV diagnostics[20]. ALP and TB serve as markers of cholestatic liver dysfunction and overall liver health[21]. While some of these biomarkers are well-established in HBV assessment, their predictive power in combination with gender has not been fully explored in a resource-limited setting like Nigeria[22]. This study aims to assess their collective utility in a predictive model to improve HBV screening and diagnosis by:

1. Developing a reliable predictive model offers several benefits:

2. Detecting HBV early using less invasive and more accessible diagnostic measures[23].

3. Identifying high-risk patients, enabling early intervention and tailored treatment plans[24].

4. Reducing economic burden on healthcare systems and patients by minimizing reliance on expensive diagnostic procedures[25].

Failure to address this gap may result in continued reliance on costly, less accessible diagnostic methods and increased HBV-related morbidity and mortality due to delayed diagnosis[26]. This study integrates demographic factors, such as gender, with serum biomarkers to predict HBV status. Predictive models that leverage clinical data offer a promising approach to HBV diagnosis, potentially improving diagnostic accuracy and enabling earlier detection[27]. Gender-specific differences and variations in serum biomarkers may also provide valuable insights into HBV infection dynamics, improving the effectiveness of predictive models[28].

Materials and Methods

The study was conducted at Enugu State University Teaching Hospital (ESUTH), Parklane, Enugu State, Nigeria. Enugu is in southeast Nigeria. Located between the Benue region and the Cross River Basin, this state belongs to Eastern Nigeria. Enugu State is ranked 29th out of 36 states in Nigeria. As of 2014, Enugu State had a population of around 3.3 million people[21].

Sample Size Estimation

The sample size was calculated using the World Health Organization's statistical method[22].

Cochran Formula: $N= (Z2Pq)/d^2$

Where:

N = sample size, Z = 1.96 (95% confidence interval), d = Sample error (5%) = 0.05, p=prevalence=11.1% (0.111) [23], and q = complementary probability=1- p=0.889

Therefore, N (1.96)2×0.111×0.889(0.05)2=152, N=152. Hence, a sample size of 152 was used in this study.

Study Participants

Hepatitis B-infected patients attending the clinic at ESUTH were recruited for the study. The sample size was determined based on statistical considerations and previous research studies.[23] Informed consent was obtained from all participants.

Inclusion Criteria

- Patients diagnosed with Hepatitis B infection.
- Patients aged 18 years and above.
- Patients willing to participate and provide informed consent.

Exclusion Criteria

- Patients with co-infection of other hepatitis viruses (e.g., Hepatitis C or Hepatitis D).
- Patients with pre-existing liver diseases or liver dysfunction unrelated to Hepatitis B.
- Patients with a history of liver transplantation.
- Patients with a history of significant alcohol consumption or substance abuse.

Patient Selection

Patients who met the inclusion criteria were consecutively recruited until the required sample size was obtained. Patients were informed about the research purpose and provided consent. Each patient was identified properly, using unique identifiers such as gender and hospital number. Patients were instructed to avoid certain medications and foods before a hepatic function panel to ensure specimen integrity. A skilled healthcare professional cleansed the skin at the venipuncture site with an antiseptic solution. A tourniquet was applied to enhance vein visibility, and blood was extracted from the inner elbow. Blood samples were appropriately labeled, stored, and handled following laboratory protocols before HBV, ALT, AST, ALP, and Alpha Glutathione S-Transferase (α-GST)[24] analysis.

Sample Analysis

Four parameters were analyzed: Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP), Alpha Glutathione S-Transferase (α-GST)

1. Alanine Transaminase (ALT)

Method of Estimation: Colorimetric method[25].

2. Aspartate Transaminase (AST)

Method of Estimation: Colorimetric method[25].

3. Alkaline Phosphatase (ALP)

Method of Estimation: Colorimetric method[26].

4. Alpha Glutathione S-Transferase

α-GST was determined based on its enzymatic activity, specifically its ability to catalyze the conjugation of glutathione (GSH) with electrophilic compounds. This conjugation process results in a glutathione conjugate, which is less toxic and more water-soluble than the parent compound. [27]

Method for α-GST Estimation: ELISA-GST, Human serum & plasma for Research Use Only.

Ethical Considerations

Ethical approval was obtained from the Research and Ethical Committee of the College of Medicine, Enugu State University Teaching Hospital (ESUTH). The study was conducted in accordance with the ethical guidelines and regulations. Informed consent was obtained from all study participants before their inclusion in the research.

Data Analysis

Chi-Square test was used as the statistical tool, and a Binary Logistic Regression analysis was performed to develop a predictive equation model. The selected predictors were analyzed in relation to the participants' HBV status.

Results

A prediction model for HBV status was developed using gender and serum levels of alpha glutathione S-transferase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase in patients attending Enugu State University Teaching Hospital, Nigeria. To construct the model, HBV status was regressed on these predictors using binary logistic regression. The analysis indicated that AST was a significant predictor of HBV status (Chi-Square = 93.939, df = 5, $p < 0.001$) (Table 1).

Table 1: Omnibus Tests of Model Coefficients

Step	Chi-square	Df	Sig.
Step	93.939	5	0
Block	93.939	5	0
Model	93.939	5	0

The other predictors, i.e., gender, GST, ALP, and ALT, were not statistically significant. AST remained significant at the 5% level (Wald = 32.894, $p < 0.001$). The odds ratio for AST was 0.895 (Table 2).

Table 2: Variables in the Equation

Variables	B	S.E.	Wald	Df	Sig.	Exp(B)
GENDER (1)	0.116	0.3	0.15	1	0.699	1.123
GST	-0.027	0.019	1.995	1	0.158	0.974
ALP	-0.006	0.004	2.173	1	0.14	0.994
ALT	0.019	0.033	0.347	1	0.556	1.02
AST	-0.111	0.019	32.894	1	0	0.895
Constant	3.272	0.649	25.4	1	0	26.362

Note: Variables entered at Step 1: Gender, GST, ALP, ALT, AST.

Prediction Equation for HBV Status

Based on the variables in the equation (Table 2), the probability model is expressed as:

$Z = b_0 + b_1 x_1$

Where:

Z = Probability of being Hepatitis positive

$b_0 = 3.272$ (Intercept)

$b_1 = -0.111$ (Coefficient of AST)

X_1 = AST

Thus, the prediction model is:

$Z = 3.272 - 0.111 \times AST$

P (Hepatitis B Positive Status) = 3.272 - 0.111 x AST = 11%

Discussion

This study aimed to develop a predictive model for hepatitis B virus (HBV) status among patients at Enugu State University Teaching Hospital, Nigeria, by analyzing the impact of gender and serum biomarkers, including alpha glutathione S-transferase (α-GST), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). The findings identified AST as the most significant predictor of HBV status, highlighting its potential role in predictive modeling.

The predictive value of serum biomarkers in HBV status has been well-documented. While previous studies have emphasized ALT as a key biomarker for HBV activity and liver inflammation [28], our findings suggest that AST may be a more relevant predictor in this cohort, aligning with research by Lok et al. [29], which identified AST as a marker of liver fibrosis in HBV-infected individuals. This supports the notion that AST could serve as an essential indicator of HBV-related liver damage.

Conversely, α-GST and ALP did not emerge as significant predictors in this study, diverging from findings by Zhang et al.[30] and Garcia et al.[31], which linked these biomarkers to liver oxidative stress and cholestasis, respectively. The differences in study population characteristics, methodology, and clinical settings may explain these discrepancies. Similarly, gender was not a significant predictor of HBV status, consistent with reports suggesting that while gender may influence HBV progression and treatment response [32], it may not independently predict infection status[33].

The identification of AST as a significant predictor underscores its potential in enhancing HBV predictive models. Future research should explore the integration of additional variables, such as HBV genotype and patient demographics, to improve predictive accuracy. Longitudinal studies are also warranted to examine biomarker dynamics over time and under varying clinical conditions. While AST plays a crucial role, further investigation is needed to elucidate the contributions of other biomarkers and demographic factors in HBV prediction.

Conclusion

This study developed a predictive model for HBV status using gender and serum biomarkers among Enugu State University Teaching Hospital patients. AST emerged as the most significant predictor among the variables examined, reinforcing its clinical relevance in HBV diagnostics. This finding aligns with existing literature highlighting AST as a key indicator of liver pathology in HBV infection[34]. While ALT, ALP, and α-GST have been implicated in HBV-related liver dysfunction[35], their predictive value was not statistically significant in this cohort. Similarly, gender did not demonstrate predictive utility, suggesting that its role in HBV status may be influenced by other factors rather than serving as an independent predictor. These findings highlight AST as a key biomarker for predicting HBV status, while the other biomarkers and gender exhibited limited predictive value. This predictive model can aid clinicians in early HBV detection, enabling timely intervention and improved patient outcomes, particularly in resource-constrained healthcare settings lacking advanced diagnostic tools.

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Conflicts of Interest: The authors declare no conflict of interest. For a written confirmation, contact the editorial office.

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