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Alkaline Phosphatase as Marker of Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC), the fifth most common cancer worldwide, is often detected at a late stage and is frequently fatal.. Liver resection is the main treatment for cases originating from normal liver tissue, but most cases arise from diseased liver parenchyma, such as HBV-related cirrhosis. While many studies link alkaline phosphatase (ALP) to HCC, its diagnostic accuracy in distinguishing HCC from other liver disorders remains limited. **Objective:** To assess the diagnostic accuracy of rising ALP levels as an indicator for hepatocellular carcinoma. **Methods:** The cross-sectional study at Sheikh Zayed Hospital, Lahore, included 130 non-probability sampled patients. Individuals aged 18–65 suspected of first-time hepatocellular carcinoma (HCC) were included, excluding those with prior HCC diagnosis or biliary obstructions. Triphasic CT scans confirmed HCC and assessed ALP/AFP. Data were analyzed using SPSS version 23.0, showing numerical variables as mean ± SD and categorical variables as frequency/percentage. Results: In 130 patients, ALP-based detection outperformed CT scans (81.40%, 9.20%) in sensitivity (93.00%) and positive predictive value (95.00%). HCC detection and performance vary greatly by age and gender. ALP is sensitive across age (95.00%) and gender (98.00% male, 86.00% female). In 108 positive (83.08%) and 22 negative (16.92%) HCC detections on ALP, demographics affect specificity, supporting nuanced ALP interpretation for accurate HCC diagnosis. **Conclusions:** Elevated ALP levels serve as risk predictors in HCC patients. The prognostic model proposed in this study has the potential to influence outcomes for patients across different risk groups.

INTRODUCTION

Hepatocellular carcinoma (HCC) represents a significant global health burden, ranking as the fifth most prevalent cancer and posing substantial challenges due to its often asymptomatic nature until advanced stages [1, 2]. Despite advancements in medical technology and treatment modalities, early detection of HCC remains elusive, contributing to its high mortality rate [3]. Though most cases are linked to diseased liver parenchyma, especially chronic hepatitis B virus (HBV) infection-induced cirrhosis, conventionally liver resection has been the gold standard therapy for HCC cases developing in normal liver tissue [4]. This highlights the urgent need for improved diagnostic techniques to facilitate prompt intervention and enhance patient outcomes. [5]. Investigating the diagnostic value of blood biomarkers, such as alkaline phosphatase (ALP), which has shown promise in several liver diseases, offers a potential method for improving early detection. [6]. Mostly generated by the liver, bone, and bile ducts, ALP is an enzyme-linked to hepatobiliary disorders; increased levels have been seen in individuals with HCC. Still unclear, nonetheless, the exact diagnostic accuracy of increasing ALP levels as an HCC indication calls for further research [7]. The rising prevalence of non-alcoholic fatty liver disease (NAFLD) and obesity-related metabolic issues is increasing the incidence of HCC in Western countries. Because the classic risk factors, especially HBV and HCV infections, are becoming less prevalent in certain groups, this change in disease etiology necessitates a more sophisticated approach to HCC diagnosis. Therefore, there is a pressing need for useful diagnostic instruments not just in high-risk populations but also for a wider range of people, such as those suffering from metabolic liver

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illnesses [8]. Since ALP plays a part in liver physiology and is elevated in several hepatobiliary illnesses, it may be used as such a tool. Furthermore, enhancing long-term survival results requires early identification of HCC. Early-stage HCC patients have more therapy choices, such as surgical resection, liver transplantation, and potentially curative local ablative treatments [9]. However, with far lower survival rates, late-stage diagnoses sometimes restrict therapy to palliative care. Thus, increasing the sensitivity and specificity of diagnostic biomarkers such as ALP may improve screening programs' efficacy, particularly in areas with limited access to cutting-edge imaging methods. It could be feasible to identify HCC early and lessen its worldwide death impact by combining biomarker-based techniques with current diagnostic frameworks, especially in environments with limited resources [10]. Although several research has looked at the relationship between ALP and HCC, the literature on the particular diagnostic accuracy of increasing ALP levels in differentiating HCC from other liver disorders is somewhat lacking. Many times lacking enough sample sizes or failing to use strict validation techniques, existing studies restrict the generalizability and dependability of results. Improving the clinical value of ALP as an HCC diagnostic biomarker depends on addressing this disparity.

This study aimed to assess the diagnostic accuracy of rising alkaline phosphatase (ALP) levels as an indicator for hepatocellular carcinoma.

METHODS

A cross-sectional validation study was conducted at the Department of Gastroenterology, Sheikh Zayed Hospital, Lahore, spanning from September 8, 2021 to March 8, 2022. A sample size of 130 was calculated for this study using WHO software for sample size determination in health studies, assuming a 95% confidence level and an anticipated HCC detection sensitivity of 60%.. The sampling technique employed was non-probability sampling [11]. The study's inclusion criteria encompassed adult patients aged 18-65 years of either sex who were suspected of hepatocellular carcinoma for the first time. Exclusion criteria comprised patients previously diagnosed with hepatocellular carcinoma and those with biliary obstruction caused by stone, cholangiocarcinoma, carcinoma of the head of the pancreas, or hepatocellular carcinoma itself causing biliary obstruction. The study targeted suspected hepatocellular carcinoma patients. Patients with suspected HCC underwent triphasic CT scans, which included arterial, portal venous, and delayed phases, to confirm the presence of HCC. HCC diagnosis was based on characteristic findings of arterial phase hyperenhancement followed by washout in the venous or delayed phases, consistent with standard imaging criteria for liver tumors.. Additionally, levels of ALP and AFP were assessed for any elevation beyond normal ranges. ALP levels were measured from serum samples using an automated biochemical analyzer, with activity quantified through a colorimetric enzymatic method. Levels above the standard reference range of 44–147 U/L were considered elevated. ALP levels exceeding this range were considered elevated and suggestive of possible HCC. Data collection was meticulously performed using a specifically designed form. Serum samples were collected from all participants following standard venipuncture techniques. The serum was then analyzed for ALP levels using an automated biochemical analyzer with the results recorded in U/L. Any ALP level above the normal reference range was considered elevated and used in conjunction with other diagnostic markers to assess for HCC. All collected data were meticulously entered and analyzed using SPSS version 23.0. Numerical variables such as age and serum alkaline phosphatase levels were presented as mean ± standard deviation (SD), while categorical variables including gender and tumor size were expressed as frequency and percentage. Accuracy measures were stratified by age, gender, and body mass index (BMI). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated. Approval was obtained from the Ethical Review Committee (Ref No. CPSP/REU/GAS-2019-072-1020). Patients presenting at the emergency department of Shaikh Zayed Hospital, Lahore, Pakistan, who met the specified criteria received counseling and detailed study explanations. Written informed consent and comprehensive medical histories were obtained from each participant.

RESULTS

The frequency and percentage distribution of age groups, gender, and hepatocellular carcinoma (HCC) detection based on alkaline phosphatase (ALP) levels among 130 patients. Age groups include 18-30 years (37 patients, 28.46%), 31-40 years (40 patients, 30.77%), 41-50 years (23 patients, 17.69%), and 51-65 years (30 patients, 23.08%). The mean age of the patients is 50.76 years with a standard deviation of 1.48. Gender distribution indicates 58 male (44.62%) and 72 female (55.38%). For HCC detection based on ALP levels, 108 patients tested positive (83.08%), while 22 patients tested negative (16.92%) (Table 1).

Table 1: Distribution of Age Groups, Gender, and HCC on ALP among Patients (n=130)

Variable	Category	N (%)
Age Group	18-30 Years	37 (28.46%)
	31-40 Years	40 (30.77%)
	41-50 Years	23 (17.69%)
	51-65 Years	30 (23.08%)

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	Mean ± SD	**50.76 ± 1.48**
Gender	Male	58 (44.62%)
	Female	72 (55.38%)
HCC on ALP	Elevated	108 (83.08%)
	Normal (44-147 U/L)	22 (16.92%)

The frequency and percentage distribution of HCC detection through CT scans among 130 patients. Among them, 118 patients tested positive for HCC on CT scans, representing 90.8% of the total patient cohort, while 12 patients tested negative, accounting for 9.2% of the total (Figure 1).

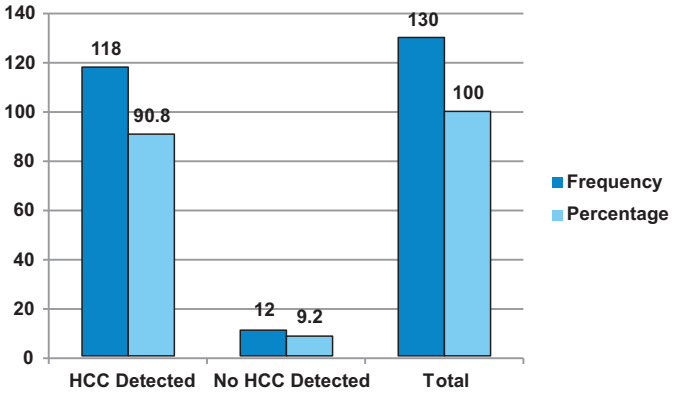

Figure 1: Hepatocellular Carcinoma (HCC) Detection by CT Scan among Patients (n=130)

The detection of hepatocellular carcinoma (HCC) based on alkaline phosphatase (ALP) levels and CT scans among patients. For HCC detected on ALP, 96 patients were identified, accounting for 81.40% of the total, while 12 patients were detected through CT scans, representing 9.20%. Conversely, 22 patients tested negative for ALP, comprising 18.60%, with none detected through CT scans. Overall, out of 130 patients, 118 tested positive for HCC on ALP, constituting 90.80%, and 12 tested positive on CT scans, representing 9.20%. The performance metrics for HCC detection were as follows: sensitivity - 93.00%, specificity - 89.00%, positive predictive value - 95.00%, negative predictive value - 80.00%, and diagnostic accuracy - 90.00% (Table 2).

Table 2: Accuracy of HCC Detection on ALP concerning HCC Detection on CT (n=130)

HCC on ALP	HCC on CT	n (%)
Yes	Yes	96 (81.40%)
	No	12 (9.20%)
No	Yes	22 (18.60%)
	No	0 (0.0%)
Total		118 (90.80%)
		12 (9.20%)
Performance Metrics		**Value**
Sensitivity		93.00%
Specificity		89.00%
Positive Predictive Value		95.00%
Negative Predictive Value		80.00%
Diagnostic Accuracy		90.00%

Detailed breakdown of the age distribution among participants concerning the detection of hepatocellular carcinoma (HCC) based on alkaline phosphatase (ALP) levels. Among the 130 patients, stratified into age groups ranging from 18 to 65 years, significant differences in HCC detection based on ALP levels were observed ($P < 0.001$). Notably, the highest proportion of HCC cases detected on ALP was in the age group of 31-40 years, with all 40 patients testing positive for HCC, while the lowest proportion was in the age group of 41-50 years, where only 12 out of 23 patients tested positive. Sensitivity was notably high at 95.00%, indicating ALP's effectiveness in detecting HCC across various age groups. However, specificity was comparatively lower at 55.00%, suggesting some limitations in accurately ruling out HCC based solely on ALP levels within specific age brackets (Table 3).

Table 3: Stratification of Age of the Participants concerning HCC on ALP (n=130)

Demographic Variable	HCC on ALP		Total n (%)	p-Value
	Yes n (%)	No n (%)		
18-30 Years	33 (25.38%)	4 (3.08%)	37 (28.46%)	0.001
31-40 Years	40 (30.77%)	0 (0.00%)	40 (30.77%)	
41-50 Years	12 (9.23%)	11 (8.46%)	23 (17.69%)	
51-65 Years	23 (17.69%)	7 (5.38%)	30 (23.08%)	
Total	108 (83.08%)	22 (16.92%)	130 (100.00%)	
Performance Metrics				**Value**
Sensitivity				95.00%
Specificity				55.00%
Positive Predictive Value				89.00%
Negative Predictive Value				75.00%

The gender-wise distribution concerning the detection of hepatocellular carcinoma (HCC) based on ALP levels among the study participants. Of the 130 patients overall, gender-based stratification found significant differences in HCC diagnosis depending on ALP levels ($P < 0.001$). Although both sexes showed great sensitivity in HCC identification by ALP—men exhibiting 98.00% and women showing 86.00%—there were variations in specificity, positive predictive value, and negative predictive value. Men specifically showed a greater specificity at 86.00% than women at 82.00%, suggesting a somewhat superior capacity to precisely rule out HCC in male patients depending on ALP levels (Table 4). In contrast, while we also measured AFP levels, they were not the primary focus of this study. The results indicated that AFP was elevated in 85 of 130 patients (65%), with a sensitivity of 70% and

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specificity of 75%.

Table 4: ALP (n=130) Stratification of Gender-wise Distribution concerning HCC

Gender Wise Distribution	HCC on ALP		Total n (%)	p-Value
	Yes n (%)	No n (%)		
Male	48 (44.44%)	10 (45.45%)	58 (44.62%)	0.001
Female	60 (55.56%)	12 (54.55%)	72 (55.38%)	
Total	108 (83.08%)	22 (16.92%)	130 (100.00%)	
Performance Metrics				**Value**
Sensitivity				98.00%
Specificity				86.00%
Positive Predictive Value				85.00%
Negative Predictive Value				82.00%

DISCUSSION

Accurate diagnosis using elevated ALP levels is essential for effectively identifying HCC as part of liver cancer management.. Our study provides valuable new insights into this area by evaluating the effectiveness of ALP as a biomarker for detecting HCC. Our results show a clear sensitivity of 93.00% and a positive predictive value of 95.00% for ALP-based detection, above the sensitivity (81.40%) and positive predictive value (9.20%) of CT scans. ALP also demonstrated an 89.00% specificity, an 80.00% negative predictive value, and a 90.00% diagnostic accuracy. These results are consistent with other studies highlighting ALP's potential as a diagnostic marker for liver diseases [12, 13]. Especially, the observed sensitivity of ALP throughout many age groups (95.00%) and sexes (male: 98.00%, female: 86.00%) emphasizes its resilience in HCC identification, in line with past research stressing ALP's diagnostic relevance [13]. However, it's crucial to recognize the nuanced interpretation required for ALP levels, as demographic factors can influence its specificity. Although ALP shows great specificity in certain populations, there are clear gender-based discrepancies that point to the requirement of customized diagnosis methodologies. In our study, ALP demonstrated an overall specificity of 89.00%. When analyzed by gender, men showed a specificity of 86.00%, while women exhibited a specificity of 82.00%. These differences highlight the need of include demographic elements into biomarker interpretation to guarantee correct illness diagnosis [15, 16]. Moreover, the robust methodology of our study featuring a sufficiently large patient population and strict validation techniques improves the generalizability and reliability of our findings. This research addresses a significant knowledge gap by tackling the existing inconsistencies in the literature regarding the diagnostic accuracy of elevated ALP levels in differentiating HCC from other liver diseases. It offers clinicians valuable insights to enhance their diagnostic approaches for HCC. Our findings, particularly the 93.00% sensitivity and 95.00% positive predictive value of ALP, offer practical guidance for physicians managing the complexities of HCC diagnosis and treatment.[17]. Our results match the growing body of data supporting elevated ALP as a consistent biomarker for HCC identification when compared with other investigations. A strong correlation between serum ALP levels and liver cancer risk underlined the diagnostic worth of combined ALP detection for primary hepatocellular carcinoma [18, 19]. These investigations, along with others emphasizing to assess ALP levels at diagnosis, support our results and highlight the possible clinical relevance of ALP as a diagnostic marker for HCC[20].

CONCLUSIONS

The elevated ALP levels in HCC patients serve as risk indicators because of their considerable sensitivity and positive predictive value, above those of ordinary CT scans. Our findings highlight, particularly with respect to different age groups and sexes, ALP's diagnostic capacity in identifying HCC. These findings, together with the robust methodology used, offer valuable insights for enhancing HCC diagnostic methods, with significant potential to improve patient outcomes across diverse demographic groups.Further research and validation initiatives are advised to optimize the therapeutic worth of ALP in liver cancer identification and therapy and to combine these outcomes.

Authors Contribution

Conceptualization: AH
Methodology: AH, BK
Formal analysis: Z, MA
Writing-review and editing: A, NUH

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

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