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ORIGINAL ARTICLE

Diagnostic accuracy of alpha-fetoprotein at various cut-off levels in hepatocellular carcinoma: A study in a tertiary health care centre, Peshawar.

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ABSTRACT… Objective: To evaluate the diagnostic accuracy of alpha-fetoprotein (AFP) at various cutoff levels in detecting hepatocellular carcinoma (HCC) and to determine the optimal AFP value for HCC diagnosis. **Study Design:** Cross-sectional study. **Setting:** Department of Interventional Radiology, Rehman Medial Institute. **Period:** May 2016 to Dec 2023. **Methods:** Utilising a dataset of 882 participants, among whom 707 were HCC positive and 175 HCC negative. The values obtained from the AFP measurements were classified into several ranges. Effectiveness of diagnostic test at various AFP cut-off points (10µg/L, 20µg/L, 100µg/L and 200µg/L) were calculated in terms of sensitivity, specificity and positive and negative predictive values. **Results:** The best sensitivity of 79.5% was obtained through the use of an AFP threshold of ≥10 ng/mL. However, this resulted in the true negative rate of 21.7%. The most sensitive cut-off value was ≥100 ng/mL for 84.2%, and the highest specificity and PPV was obtained in the cut-off at ≥200 ng/mL for 97.1% and 95.4%, respectively. This is because the AFP accuracy is not constant and varies from level, therefore, should be used in combination with other diagnostic tools. **Conclusion:** It was found that the diagnostic accuracy of AFP is different with different cut-off levels which make it appropriate for either screening or confirming diagnosis in different ways. The low cut-offs are suitable for screening, whereas the high cut-offs fit the purposes of diagnosis confirmation. Studying the correlations and combination of AFP with other diagnostic biomarkers and imaging modalities should be the direction of future studies for HCC diagnostic models.

Key words: Alpha-fetoprotein, Biomarkers, Diagnostic Accuracy, Hepatocellular Carcinoma.

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INTRODUCTION

HCC is the most common subtype of primary liver cancer, and it burdens comprehensive morbidity and mortality around the world.[1] The disease ranks fourth in the world for cancers and is one of the deadliest cancers for all patients with cancers.[2] HCC is not uniformly spread around the world; the highest incidences of HCC are found in countries with high prevalence of hepatitis B and C, such as Sub-Saharan Africa and East Asia.[3] Mostly, the reasons are associated with chronic liver diseases such as cirrhosis due to viral hepatitis, alcohol, or non-alcoholic fatty liver disease (NAFLD).[4] Despite the development of new technologies in medical sciences and clinic medicine, the outlook for HCC till the present moment remains rather grim mainly because of the gap between the time of diagnosis and the optimal moment for treatment and the complex organology of liver tissue.[5]

HCC is not easy to diagnose and there are many factors that contribute to it.[6] The first signs of HCC are often nonspecific and may not be manifested at all in early-stage disease, while the manifestation of symptoms most often occurs in the later stages of tumor progression, thereby complicating the treatment outcomes.[7] The existing diagnostic tools include imaging tests including ultra sound, CT scan, MRI scan, and liver biopsy.[8] However, it is essential to note some of the limitations of the above methods. Imaging procedures although are less invasive and can give complete image of the liver but can miss tiny nodules whereas liver biopsy, which is invasive and the gold standard, has complications including bleeding and can give a skewed picture if the biopsy sample is taken from an abnormal area of the liver.[9]

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As a result, the identification of accurate, minimally invasive molecular signatures that would allow for quicker identification and assessment of HCC progression is imperative.[10] AFP is a glycoprotein generated by the fetal liver and has been found to be useful and investigated widely as a marker for HCC.[11] The abnormal levels of the factor AFP in adults can be a sign of liver malignancy, that is why this factor is important in using the diagnostics of HCC.[12] Nevertheless, the performance of AFP in its diagnostic ability has remained inconclusive because of the fluctuations of sensitivity and specificity found at the various cut-off points.[13] Even though AFP testing is easily done and inexpensive, the performance of AFP testing rises problems involving existence of False positive/False negative results that should be improved by finding the best cut-off values of diagnosing cancerous cells accurately. It is within this context that this research seeks to bridge the existing knowledge on the diagnostic efficiency of AFP at different cut-off points to optimise screening and management of HCC.[14] However, in fetal life, the role of AFP is similar to that of albumin because the protein is involved in the transportation of several substances such as metals, fatty acids and bilirubin.[11] It also has an immunosuppressive effect, whereby it is used to shield the fetus from the mother's immune system. Consequently, AFP levels decrease steadily and are generally undetectable in adults whose baby is otherwise healthy. It is, therefore, possible to infer that 'high' levels of AFP in adults can be associated with pathological conditions, especially those involving the liver.

AFP has been considered to be useful as a biomarker for HCC due to its higher level in most patients with this cancer.[11] The use of AFP in HCC diagnosis is well founded as hepatoma cells are known to produce this fetal protein which is not normally seen in adult livers.[15] Conventionally, AFP testing has been regarded as one of the most widely applied blood tests for patients with a probable liver cancer. Its role is important especially in the areas where Liver cancer is common and where application of advanced imaging techniques might not be readily available.[16] The advantage of using AFP as a biomarker is therefore based on the non-invasive approach, ability to measure it and the relatively cheap method of diagnosis compared to other modalities.

Even though AFP is known to be a reliable marker for various cancer types, the current literature is still inconclusive about the diagnostic performance of the test. It should be noted that AFP can be raised in conditions other than liver cancer such as chronic hepatitis and cirrhosis, acute hepatitis, and other liver diseases, leading to false positive results.[17] On the same note, not all HCC patients have problematic AFP levels and this often leads to false negative results. This shows that AFP is very sensitive and specific when used as a diagnostic marker but this is highly dependent on the upper and lower normal levels used in analysing the results. By using a low cut-off, the test has increased sensitivity but decreased specificity, while the high cut-off improves the specificity but has decreased sensitivity. These findings highlight the usefulness of AFP levels as a qualifier in specific situations and the importance of combining it with other tests.

The developments in HCC research in the last recent has also demonstrated that there is a possibility of adding some other biomarkers and imaging to improve the diagnosis rates of the disease besides use of AFP. This is because additional protein of AFP that has been modified by the deletion of gamma carboxy prothrombin or that has been bound with lens culinaris agglutinin is useful in increasing the specificity and sensitivity of the disease detection.[18] The current study seeks to replicate and extend earlier findings on the diagnostic psychometric properties of AFP when used at different cut-off values in a clinical setting and, thus, identify theoretical and practical enhancements for integrating it in screening for HCC.

METHODS

The present study utilizes a cross-sectional research design to determine the diagnostic likelihood of AFP at different cut points in HCC. This study was done in interventional radiology department of Reham Medical Institute after approval from ethical committee (RMI/RMI-REC/Article Approval/118/04-7-24), Peshawar form May 2016 to Dec 2023. The study sample comprises a total of 882 participants: 707 patients with confirmed

HCC, 175 patients without HCC. These patients were selected based on medical records from our HMIS (health Management information system) and PACS (Picture archiving and communication system). A total of 882 patients were enrolled in the study because they all had undergone AFP testing in the context of liver diseases. HCC diagnosis was made through typical imaging features on computed tomography (CT) and magnetic resonance imaging (MRI) with supporting tumor markers. In patients whose imaging features were inconclusive then ultrasound guided biopsy with histopathological analysis done. The conditions included non-malignant liver diseases in patients with non-HCC cancer being ruled out during follow-up tests. Moreover, serum concentrations of the AFP were determined by enzyme immunoassay, which is a reliable, sensitive and specific technique for assessment of AFP levels as used in this study. Furthermore, to evaluate the performance of the density of AFP at different cutoff points, different statistical measures like sensitivity that measures the ability of the density of AFP to identify actual HCC patients, specificity that measures the ability of the density of AFP to identify actual non-HCC patients, positive predictive value that estimates the probability of HCC in patients with a positive test result, negative predictive value that estimates the probability of no HCC in patients with a negative test.

These metrics were evaluated at four specific AFP cutoff levels: 10 nanograms per milliliter, 20 nanograms per milliliter, 100 nanograms per milliliter, 200 nanograms per milliliter. The conventional formulas were used to compute the sensitivity and specificity:

- Sensitivity = (True Positives) / (True Positives + False Negatives)
- Specificity = (True Negatives) / (True Negatives + False Positives)

While, the PPV and NPV were derived from the sensitivity, specificity, and the prevalence of HCC in the study population:

- PPV = (Sensitivity * Prevalence) / [(Sensitivity * Prevalence) + (1 - Specificity) * (1 - Prevalence)]
- NPV = [Specificity * (1 - Prevalence)] / [(Specificity * (1 - Prevalence)) + ((1 - Sensitivity) * Prevalence)]

We employed OpenAI's Chat GPT to help to improve the manuscript's coherence and clarity, within limitation of ethical standards. Lastly, the statistical investigations were performed with SPSS v27 software. For demographic data, the results were shown in frequency and percentage whereas for quantitative data, they used Mean and Standard Deviation. The diagnostic performance of each AFP cut-off level was also presented in tabular form, which displayed the true positive and true negative rates of each threshold depending on the preferred balance between sensitivity and specificity. This approach enables the development of a more elaborate recognition of AFP within the conceptualization of HCC and contribution in discovering the ideal cut-off points for a various setting.

RESULTS

AFP is a crucial biomarker in the diagnosis of HCC. This analysis is based on assessing the performance of AFP at different thresholds regarding the diagnosis of HCC and identification of the best AFP cut-off level for diagnosing it. From the dataset of 882 patients, 707 were diagnosed with HCC, and 175 were without HCC. The distribution of AFP levels among these patients is categorized into several ranges as depicted in the table 1 below.

TABLE-I

Distribution of AFP levels in diagnosis

AFP Level	Patients With HCC	Patients Without HCC
AFP < 10 ng/mL	145	137
AFP 11-20 ng/mL	51	9
AFP 21-40 ng/mL	52	9
AFP 41-100 ng/mL	67	5
AFP 101-400 ng/mL	102	8
AFP 401-2000 ng/mL	119	1
AFP > 2000 ng/mL	155	5

A sizeable subgroup of HCC patients even had AFP levels lower than 10 ng/mL, regarded as negative in the traditional sense. In total, only 145/707 of HCCs had AFP levels <10 ng/mL, which means that theoretically, about 20.5% of the assumed HCCs would not have been diagnosed when based only on AFP. At various cutoff points,

the diagnostic performance of AFP was assessed using the following metrics: sensitivity, specificity, (NPV), (PPV), and positive predictive value (NPV). 10 ng per millilitre, 20 ng per millilitre, 100 ng per millilitre, and 200 ng per millilitre are the cutoffs that were evaluated. AFP With a sensitivity of 79.5%, a threshold of 10 ng per millilitre can detect the majority of HCC patients. However, its low specificity (21.7%) indicates a high rate of false positives, making it less useful for definitive diagnosis without further confirmatory tests. While, AFP Cut-off of 20 ng/mL exhibits a moderate increase in specificity (43.4%) with a slight decrease in sensitivity (71.7%) suggests a better balance for screening purposes, but it still includes a considerable number of false positives. Similarly, AFP threshold of 100 ng/mL offers a much higher specificity (94.8%) and PPV (93.1%), indicating that patients with AFP levels above 100 ng/mL are very likely to have HCC. The sensitivity drops to 53.5%, indicating a higher risk of missing HCC cases with lower AFP levels. Lastly, AFP threshold of 200 ng/mL shows the highest specificity (97.1%) and PPV (95.4%) at this level make it highly reliable for confirming HCC diagnosis when AFP is elevated. However, the low sensitivity (39.0%) indicates that many HCC cases with AFP below 200 ng/mL would be missed. The result summary can be seen in the table 2 below;

TABLE-II

Evaluation of AFP cut off levels

AFP Level	AFP ≥ 10 ng/mL	AFP ≥ 20 ng/mL	AFP ≥ 100 ng/mL	AFP ≥ 200 ng/mL
Sensitivity	79.5%	71.7%	53.5%	39.0%
Specificity	21.7%	43.4%	94.8%	97.1%
PPV	68.5%	72.5%	93.1%	95.4%
NPV	30.9%	41.8%	61.3%	51.5%

In the context of other clinical factors such as status of Hepatitis B and C, HBV-positive patients showed higher AFP levels, aligning with the more aggressive tumor characteristics associated with HBV infection. Likewise, HCV-positive patients had a less pronounced correlation with elevated AFP levels, suggesting different mechanisms of AFP production in these infections. Furthermore, elevated bilirubin correlated with higher AFP levels, suggesting compromised liver function in more advanced HCC. While, lower serum albumin was associated with higher AFP levels, indicating poorer liver synthetic function in more aggressive HCC cases. In addition, elevated SGPT was often observed in HCC patients, reflecting liver cell damage and turnover. Moreover, higher Child-Pugh scores correlated with increased AFP levels, underscoring the link between liver cirrhosis severity and tumor aggressiveness. Similarly, as expected, higher ECOG scores correlated with a reduced survival rate, underscoring the role of general health status in HCC prognosis. Also, patients with high AFP levels had a very low life expectancy, showing that AFP is more of a prognostic marker.

In summary, the AFP cutoff for the diagnosis of HCC may also differ based on certain clinical contexts. However, lower screening levels (10–20 ng/mL) are applicable since they have a higher accuracy but at the same time have the disadvantage of possibly producing false positive results. While higher cutoffs (100–200 ng/mL) offer improved specificity and are more preferred in diagnosis than screening tests. Due to the rising number of patients with HCC and negative AFP levels, it should be noted that AFP cannot be relied on alone and should always be used in combination with other tests, such as imaging and biopsy, to enable accurate diagnosis and staging of HCC.

DISCUSSION

Our results on sensitivity and specificity of AFP at various cutoffs may be useful to understand the utility of this biomarker in HCC diagnosis. These findings are discussed in light of previous data indicating that AFP is a useful but not ideal serum biomarker of HCC. Variations in sensitivity and specificity coefficients of AFP reported by earlier workers are consistent with a relatively low discriminatory potential of this tumour marker when used singly. This study confirms these findings and highlights the concern that practice directions should be less black and white.

Our analysis displayed a sensitivity of 79.5% along with specificity of 21.7% in an AFP cutoff of 10 ng / mL, respectively. Although the rate of false positives is higher, AFP cutoffs with lower values provide higher sensitivity and are useful for screening,

according to Anwar et.al (2020).[19] The use of AFP in conjunction with other diagnostic instruments to improve accuracy was also noted.

Our sensitivity of 71.7% and specificity of 43.4% were achieved by adjusting the AFP cutoff to 20 ng / mL. Munir et.al (2021) found similar variation in AFP levels among Pakistani individuals, suggesting that moderate cutoffs may provide a more complete method for screening and diagnosis despite the risk of false positives.[20]

Our research found a rise in PPV (93.1 percent) and specificity (98.8 percent) in an AFP cutoff of 100 ng / mL along with a reduction in sensitivity (53.5 percent). This indicates that patients with higher than 100 ng / mL AFP are at increased risk for HCC. Khan et al. found similar associations between higher AFP levels and larger tumor sizes. (2022), which supports higher AFP cutoffs for more specific HCC diagnosis confirmation.[21]

We determined the highest PPV (95.4%) and specificity (97.1%) and lowest sensitivity (39%) at 200 ng / mL. Raised AFP levels have been described by Bajkani (2019) as a prognostic factor for HCC, especially in patients with chronic liver disease[22] Hence, our results suggest that high AFP cutoffs may be useful to confirm diagnoses and prognosis In more advanced cases.

Our study also identified a prognostic value for elevated AFP (> 200 ng / mL), which are associated with poorer survival. Shaikh et.al (2016) reported similar patterns, indicating that higher AFP levels are associated with higher mortality in HCC patients.[23] Bai et al. (2017) also explored the prognostic value of AFP levels, reporting that higher AFP levels at diagnosis are associated with worse pathological grades and poorer prognosis.[24]

In our study, intermediate AFP cutoffs (20-100 ng / mL) were found to be a good compromise between specificity and sensitivity that enhanced tumor detection without a high number of false positives. Sahbbir and others. both in 2019 and Laura et al. (2016) also found a correlation between HCC patients' AFP levels and tumor size and quantity, suggesting the utility of these intermediate cutoff levels for more precise tumor detection.[25,26]

Our study demonstrated that higher AFP levels are associated with more advanced disease stages and poorer liver function accompanied with elevated Child-Pugh scores and lower serum albumin. This supports the findings of Toader et al. (2019), who also noted elevated AFP levels in more aggressive tumor types, supporting AFP's significance as a marker of tumor aggressiveness and disease severity.[27]

Practical implications of the ROC curves representing the diagnostic reliability and accuracy of the test at different AFP thresholds are discussed. For example, AFP of 10 ng / mL may be sensitive but may not be appropriate for the distinction between normal and abnormal conditions due to its low specificity. This means patients may have to go through other processes that their conditions do not warrant and they become anxious as well. However in the very first round of triage where the aim is usually to identify as many HCC as possible, it can be useful, particularly for those in the community that are believed to be vulnerable to the illness. In contrast, at 200 ng / mL, its high specificity and positive predictive value establish the diagnosis of HCC.

The trade-off between the two factors when using different AFP cut-off levels should be considered. Cut offs of 10 ng / mL and 20 ng / mL are low for wishing high sensitivity to prevent HCC cases from being missed for confirmation at the cost of high specificity. Higher cut-offs such as 100 ng / mL or 200 ng / mL increase specificity, reducing false positive rates, and reducing sensitivity to possible true cases of HCC through consideration of client history and possible signs or symptoms, community prevalence rates, screening objectives rather than diagnostic goals. Lastly, because AFP is not as accurate as might be expected, its use in combination with other biomarkers or imaging studies may improve diagnostic outcome. Additionally, biomarkers such as des-gamma-carboxy prothrombin are as useful as imaging techniques such as ultrasound, CT or MRI, where an AFP level of 20 ng / mL together with features suggestive of altered imaging could improve diagnostic certainty without directly testing

with only this test.

Our research contributes to a global understanding of HCC epidemiology by revealing details about the diagnostic performance of AFP at different cutoffs and its pros and cons in different clinical settings. Toh et.al and Samant et al. (according to our results) claimed the value of biomarkers like AFP in the diagnosis & therapy of HCC.[28,29]

Gentile et.al (2017) found that greater combinations of AFP and additional markers improve diagnostic accuracy.[30] Hu et.al (2018) reported that neutrophil-to-lymphocyte ratio and AFP together confer additional diagnostic value[31] our results highlight the importance of combining AFP with other diagnostic modalities to increase accuracy and reliability when the study was limited to AFP.

We validate the combined use of AFP and imaging for accurate HCC diagnosis, and our data support this approach at higher AFP cutoffs where specificity is high, Abduljabbar (2023).[32]

Hanif et.al (2022) described the limitations of AFP as false positives and false negatives.[33] Our work underscores similar issues, with lower AFP cutoffs and the need for additional diagnostic methods to improve overall accuracy.

Finally Chang et.al. AFP measurement was promoted in cirrhosis patients' HCC surveillance, suggesting its utility for surveillance, especially at cutoff levels that compromise specificity / sensitivity.[34] This facilitates early detection and monitoring in high risk populations.

This study indicates that the diagnostic ability of AFP varies with different cut-off levels of AFP in HCC diagnosis. Low concentrations (10-20 ng / mL) provide high sensitivity and are used for first acting results with high rates of false-positives. Higher cut-off (100-200 ng / mL) provides greater specificity for diagnosis confirmation and miss of many HCC cases. These results indicate that current use of AFP as a screening tool is suitable when combined with imaging along with other biomarkers for better accuracy. The studies should involve the discovery of new biomarkers and better incorporation of newer diagnostic modalities to detect HCC earlier and to improve the survival of the patients. Clinicians should consider the trade off between sensitivity and specificity when using cut offs for AFP charting and adjust AFP threshold based on clinical context and patient characteristics.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Muhammad Abdullah:** Conception.
2	**Aman Nawaz Khan:** Design.
3	**Ummara Siddique Umer:** Acquisition of data.
4	**Muhammad Kamran Khan:** Analysis.
5	**Abdullah Safi:** Interpretation of data.