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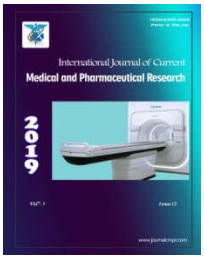

Research Article

EVALUATION OF α-L-FUCOSIDASE FOR THE DIAGNOSIS OF HEPATOCELLULAR CARCINOMA USING DIFFERENT THRESHOLDS

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ABSTRACT

Purpose: This study aimed to analyze the result of hepatocellular carcinoma (HCC) diagnosis using α-L-fucosidase (AFU) and determine the optimal scale for the threshold. **Methods:** A comprehensive literature search of PubMed, EMbase, Medline, Cochrane Library, and Google Scholar was conducted. Information regarding the threshold, sensitivity, and specificity of AFU for diagnosing HCC was extracted. Corresponding Youden's indices were derived, and ROC values were calculated using the meta-analyses method. **Results:** Sixteen studies were included in this study. When the threshold was <10 μmol/L/min or 10-20 umol/L/min, the average values of Youden's index were 0.54, and when the threshold was 30-40 and >40, the average values of Youden's index were 0.45 and 0.31, respectively. However, when the threshold was 20-30, the average value of Youden's index one was 0.62, the highest. When the threshold was 20-30, the DOR average value was also the highest. **Conclusion:** The optimal threshold was 20-30 umol/L/min in the serum AFU test for HCC diagnosis. DOR can be used as an auxiliary index with the AFU-based HCC diagnosis.

INTRODUCTION

In 2018, liver cancer morbidity and mortality ranked seventh and third among global tumors, respectively. The number of new cases of liver cancer was 841,080 and the number of related deaths was 781,631. Hepatocellular carcinoma (HCC) is associated with chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infection. Given the asymptomatic nature of early HCC and the lack of effective diagnostic and screening strategies, most patients (>80%) present with advanced HCC stages [1]. Furthermore, several cases have shown that early detection of HCC and timely treatment are critical for improving patient survival. Tumor markers are pivotal tools for the early diagnosis of tumors. Serum alpha-fetoprotein (AFP) is now widely used for clinical detection of early HCC; however, its clinical sensitivity for disease diagnosis is affected by its low sensitivity. New biomarkers are urgently needed for specific early diagnosis of HCC patients. α-L-fucosidase (AFU) is a lysosomal enzyme found in all mammalian cells. Many scholars have proposed AFU as a tumor marker for HCC diagnosis. However, many studies have shown that different cut-off values of AFU are used for HCC diagnosis. This makes people unable to choose which cut-off value in practice.

This study aimed to identify the optimal cut-off value by analyzing the accuracy of HCC diagnosis using AFU and by assessing the relationship between the cut-off value and Youden's index of AFU.

METHOD

Search and selection

All the papers published thus far in the English language were searched in the PubMed, EMbase, Medline, Cochrane Library, and Google Scholar databases. In addition, the references in the included papers were analyzed. We used the keywords "hepatocellular carcinoma," "HCC," "α-L-fucosidase," "AFU," "cut-off," and "critical." The keywords search and free word search were adopted.

The two authors (Lei Xi & Chunqing Yang) independently extracted the data from the included articles and resolved any disagreement via discussion. The following data were extracted from each article: first author, publication year, country, number of HCC cases and controls, cut-off value, and raw data (true positive [TP], false positive [FP], false negative [FN], and true negative [TN] subjects), sensitivity and specificity.

Inclusion criteria of the study

1) All samples are serum samples, 2) no treatment before sample collection, 3) testing of the diagnostic value of AFU in the HCC patients, 4) reported cut-off value, 5) sensitivity and specificity of AFU is reported or can be calculated, and 6) only

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benign liver disease or other malignant liver cancer in the controls.

Exclusion criteria of the study

1) Sample collected from a tissue or another body fluid (i.e., not a serum sample), 2) received treatment before sampling 3) data on cut-off value, sensitivity, and specificity not available, 4) animal study, 5) control group comprised healthy individuals or was absent, or6) all patients in the experimental group diagnosed with HCC using gold standard assessment.

RESULTS

We retrieved 167 related articles in our search. After removing the duplicates, 84 articles remained, of which 21 were eligible for full-text evaluation. Five articles were excluded as per the inclusion and exclusion criteria, and the remaining 16 articles [2-17] were included in our analyses. The characteristics of the included articles are shown in Table 1. These articles involved a total of 2,122 patients, of which 978 had HCC and were in the experimental group, while 1144 did not have HCC and were in the control group.

As can be seen from Table 1, six articles were from studies conducted in Egypt, four were from those in China, two were from studies done in Japan, and four articles were from those performed in South Africa, Italy, England, and Thailand, respectively. All the articles reported the cut-off value and raw data for AFU-based HCC diagnosis.

Table 1 Main features of the selected articles

Author, year	Country	HCC/ control	Cut- off*	TP	FN	FP	TN	Sens.	Spec.	Youden's index
Shao,09	China	30/30	40.00	20	10	12	18	0.667	0.600	0.27
Zhu,13	China	113/102	10.61	64	49	18	84	0.582	0.824	0.41
Zhang,15	China	116/104	40.80	80	34	40	69	0.702	0.633	0.34
Wang J,04	China	148/218	37.00	125	23	33	185	0.791	0.889	0.68
El-houseini,01	Egypt	50/50	10.00	35	15	7	43	0.700	0.860	0.57
El-houseini,05	Egypt	44/20	3.66	36	8	9	11	0.818	0.550	0.38
Montaser,12	Egypt	40/40	2.30	36	4	4	36	0.900	0.973	0.80
El-tayeh,12	Egypt	37/59	5.79	27	10	8	57	0.730	0.877	0.62
Habachi,18	Egypt	86/89	37.00	61	25	45	44	0.709	0.494	0.21
Mossad,14	Egypt	40/30	25.00	35	5	4	36	0.875	0.900	0.78
Marotta,91	Japan	19/30	12.33	16	3	3	27	0.842	0.900	0.74
Takahashi,94	Japan	67/47	8.60	52	15	10	37	0.776	0.787	0.55
Bukofzer,89	South Africa	72/64	25.00	54	18	19	45	0.750	0.703	0.45
Giardina,92	Italy	21/76	7.47	16	5	7	69	0.762	0.908	0.63
Hutchinson,91	England	35/35	7.26	21	14	12	23	0.600	0.657	0.26
Tangkijvani,99	Thailand	60/150	14.50	49	11	44	106	0.817	0.707	0.43

*: umol/L/min; Sens.: sensitivity; Spec.: specificity.

ANALYSIS

Statistical analyses

Based on the data on sensitivity and specificity obtained previously, we calculated the corresponding Youden's index values. The Youden's index is the sum of sensitivity and specificity minus one. The larger the index, the better the effectiveness of the screening experiment and the greater the authenticity.

We also calculated the corresponding diagnostic odds rate (DOR) using the meta-analyses method [18, 19]. DOR is the integration of sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio into a single indicator. It indicates that the chance of a positive result in a diagnostic test is a multiple of that of a negative result. It is a commonly used indicator in data analyses.

After obtaining the data for the cut-off values and the corresponding Youden's indices, we divided the secut-off values into five groups as follows: <10umol/L/min, (10 ≤ x<20) umol/L/min, (20 ≤ x<30)umol/L/min, (30 ≤ x<40) umol/L/min, and (40 ≤ x<50) umol/L/min. Then, the average values of Youden's index and DOR were calculated, corresponding to the five groups. The results are shown in Table 2. For reference, we also calculated the corresponding average cut-off value.

Table 2 Index conditions at different cut-off values

Cut-off	v < 10	10 ≤ v < 20	20 ≤ v < 30	30 ≤ v < 40	40 ≤ v < 50
Youden's-average	0.54	0.54	0.62	0.45	0.31
DOR-average	25.5	19.79	35.05	16.43	3.53
Cut-off-average	5.84	11.86	25	37	40.4

Diagnosis of HCC based on different AFU thresholds

As can be seen from Table 2, when the threshold was<10 umol/L/min and 10-20 umol/L/min, the average value of Youden's index was 0.54; when the threshold was 30-40umol/L/minand>40umol/L/min, the average values of Youden's index were 0.45 and 0.31, respectively. However, when the cut-off value was 20-30umol/L/min, the average value of Youden's index was 0.62, the highest. This means that the sum of the sensitivity and specificity was also the highest. Therefore, we believe that the most suitable scale for the cut-off value is 20-30 umol/L/min for the serum AFU test in HCC diagnosis. And, we can determine that when the cut-off value is in the highest range, the DOR average value is also the highest.

This suggests that we can also use DOR as an auxiliary index with serum AFU test for HCC diagnosis.

DISCUSSION

HCC is the leading cause of death in patients with chronic liver disease. HCC usually develops in an orderly progression from hepatitis to cirrhosis to early cancer. Serum marker assays show many advantages over histopathological examination. Therefore, we need to find more sensitive and specific HCC tumor markers. In many studies, AFU has been proposed as a serum marker for HCC. Patients with healthy and benign liver disease have lower AFU concentrations, while those with HCC have higher AFU levels[18]. However, the value of serum AFU for detecting early-stage HCC is limited because contradictory results have been reported[13]. Further, different cut-off values of AFU have been reported in the literature.

Some studies have attempted to increase the positive rate of HCC by combining AFU with other methods of examination.

For example, the combination of AFU and AFP may improve the diagnostic value [3,4, 6, 7]. In particular, El-Houseini (2001) reported that simultaneous determination of AFP and AFU can improve HCC diagnosis in patients with cirrhosis. Tangkijvanich *et al*. (1999) considered AFU to be a useful marker in conjunction with AFP and ultrasonography for detecting HCC, particularly in patients with underlying viral hepatitis and cirrhosis.

In addition, four studies have shown that the combination of AFU with other tumor markers can improve the diagnostic accuracy of HCC [13, 14]. For example, Zhu *et al*. (2013) reported that GGT-II combined with AFU or AFP has higher sensitivity and specificity for HCC diagnosis. Zhang (2015) evaluated the diagnostic efficiency of HCCin a combined analysis of AFU, AFP, and thymidine kinase 1 (TK1) to find that combined detection of serum AFU, AFP, and TK1 can significantly improve the sensitivity of HCC diagnosis. Therefore, if the AFU threshold of 20-30 umol/L/min is used in combination with other diagnostic methods, the detection rate of HCC will increase significantly.

Our research is limited by the relatively small number of studies. Screening for asymptomatic populations is different from that for high-risk groups. The use of DOR as an auxiliary indicator is based on a limited amount of research; therefore, further investigation is necessary to confirm these results. In spite of these limitations, the relationship between the cut-off value and Youden's index has been established. Therefore, acut-off value range of 20-30 umol/L/min for AFU can be recommended for HCC diagnosis. Further, DOR can be used as an auxiliary index in AFU-based diagnosis of HCC.

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