Clinical Utility of Lens Culinaris Agglutinin-Reactive Alpha-Fetoprotein in the Diagnosis of Hepatocellular Carcinoma: Evaluation in a Thai Referral Population

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Background and Objective: *There is no established clinical role for the lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3%) in the management of the Thai hepatocellular carcinoma (HCC) patient population. The aim of this prospective study was to evaluate clinical utility and performance characteristics of AFP-L3% for the diagnosis of HCC in Thai referral patients.*
Material and Method: *Sixty-one histologically proven HCC patients and 35 patients with other liver cancers were included for analysis.*
Results: *The HCC population was comprised of 50 males and 11 females, with a mean age of 48.8 years. According to the Okuda system, three were classed as stage I, thirty-five belonged to stages II, and six were classified in stage III. An AFP-L3% a cut-off value of > 15% yielded a sensitivity of 82% (95% confidence interval [CI], 74-88%), specificity of 71% (95% CI, 58-82%), positive predictive value of 83% (95% CI, 75-90), and negative predictive value of 69% (95% CI, 56-80) for the diagnosis of HCC. In HCC patients with AFP of < 200 ng/ml, an AFP-L3% at a cut-off value of > 15% not only maintained high sensitivity of 83% and good specificity of 71% but also increased negative predictive value to 86% for the diagnosis of HCC.*
Conclusion : *AFP-L3% provides high sensitivity but with lower sensitivity in the diagnosis of HCC than total AFP in individuals with symptomatic liver mass. However, considering its high negative predictive value in patients with AFP < 200 ng/ml, AFP-L3% might be useful as an adjunctive marker, in combination with AFP, to exclude the presence of HCC.*

Keywords: *Alpha-fetoprotein, Hepatocellular carcinoma, Hepatitis B virus, Len culinaris*

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Hepatocellular carcinoma (HCC) is one of the leading causes of death from cancer worldwide[1]. The incidence of HCC has increased over recent years, due to the increasing prevalence of chronic liver disease from various etiologies. Chronic hepatitis particularly caused by chronic viral hepatitis infection and alcohol can progress to cirrhosis in 20-25%[2,3] of cases and is a well-established significant risk factor for the development of HCC. The early detection of HCC is an essential issue for the management of this cancer since patients diagnosed with early stage HCC can receive timely potentially curative treatments such as hepatic resection, percutaneous ablation, and liver transplantation. Unfortunately, most HCC patients are diagnosed at an advanced stage, usually when the tumor is non-resectable. Radiofrequency ablation and transcatheter

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arterial chemoembolization are considered a palliative option in these patients.

Recent advances in diagnostic imaging technology including ultrasonography, helical computed tomography (CT), and magnetic resonance (MR) imaging have facilitated the accurate diagnosis of HCC[4-6] However, the test properties of these modalities varies widely depending on the experience of the operators, and the instruments required are generally expensive. Moreover, there is difficulty in differentiating HCC from other malignant and non-malignant liver tumors based on imaging findings alone in some patients, and pathological confirmation of cancer could not obtained in some cases. Hence, there is an urgent need for improved methods of diagnosis of individuals at risk for HCC.

Alpha-fetoprotein (AFP) is an oncofetal glycoprotein that has been used as a tumor marker for HCC[7]. However, AFP is not specific for HCC and it is often elevated in patients with chronic viral hepatitis infection in the absence of cancer[8-10]. Considering the current poor performance of total AFP level in the diagnosis of HCC, has led to increased interest in identifying serum tumor markers with a potential for higher accuracy for the diagnosis of HCC. *Len culinaris*, an agglutinin-reactive AFP known as AFP-L3, which has an additional a 1-6 fucose residue appended to *N*-acetylglucosamine at the reducing end, has been reported to be a more specific marker for the diagnosis of HCC than total AFP level[11] and to be associated with more aggressive HCC in studies from Japan[12,13] and Western countries[14,15]. However, the clinical utility of AFLP-L3 percentage of total AFP concentration or AFP-L3%, in the Thai HCC population remains unknown. In order to clarify the clinical usefulness and performance characteristics of AFP-L3% in the diagnosis of HCC, a prospective study was conducted in patients having histologically proven HCC at a referral center in Thailand.

Material and Method

Patient population

Our patient population was composed of all consecutive patients having malignant liver tumors who were referred to the Liver Clinic of Medicine Department of Siriraj Hospital, Faculty of Mahidol University between June 1999 and December 2000. In all cancer patients the tumors had been detected by abdominal ultrasound studies. Each focal lesion detected was further evaluated by either multiphasic spiral CT or MR imaging. The diagnosis of HCC and other malignant liver cancers was based on histopathology in all patients. Of the 96 patients with malignant liver tumors, 61 patients (64%) had histological evidence of HCC and the remaining 35 patients (36%) had non-HCC cancers. The study was approved by the Institutional Review Board of the Hospital and written informed consent was obtained from all patients for participation in medical research.

Clinical and biochemical parameters were obtained from the patients during the admission for the liver biopsy. Variables were recorded, including patient age, gender, etiology of liver disease, symptoms and physical findings, liver function test, and hematological indices. Hepatitis B virus (HBV) infection was documented by hepatitis B surface antigen positivity. Hepatitis C virus (HCV) infection was detected by means of second generation enzyme-linked immunosorbent assay for HCV antibodies. Tumor morphology was determined based on CT or MR imaging findings. The tumor stage was based on the Okuda system[16], which determines stages by the summation of the points for four variables including tumor size, ascites, albumin, and bilirubin (Stage I, score 0; Stage II, score 1 or 2; Stage III, score 3 or 4). Furthermore, the Karnofsky Performance Status (KPS) scales (scores from 0 to 100) for general health, based on the following items were obtained[17]: severity of symptoms rated by patients themselves, activities of daily life and levels of nursing evaluated by medical staff were obtained. High KPS scores suggest good health.

All liver needle biopsy specimens were stained with haematoxylin-eosin, and each histopathological diagnosis was determined by a pathologist specializing in the liver; HCC differentiation grading is obtained according to the Four level Edmondson grading system[18]. Grade I consists of cells that are similar in size to normal hepatocytes and arranged in relatively thin trabeculae. Grade II consists of cells that are larger than normal hepatocytes with more hyperchromatic nuclei, which occupy a higher proportion of cells. Grade III consists of hepatocytes with larger nuclei which are occupying more than 50% of the cytoplasm. Grade IV consists of cells with nuclei occupying most of the cytoplasm, and the cytoplasm may not be eosinophilic. Intravascular and intrasinusoidal growth is also commonly present.

Measurement of serum AFP-L3 levels

Samples were obtained at the time of diagnosis or at the time when patients were first seen at our institution prior to treatment and immediately

stored at -80°C until use. Plasma level of AFP-L3 was measured by using lectin affinity electrophoresis with Lens culinaris agglutinin[19] (Wako Pure Chemical Industries, Ltd, Osaka, Japan). This assay uses a liquid-phase binding reaction between antigen and antibody and separates bound and free forms by column chromato-graphy[20]. Fraction of AFP-L3 was defined as percentage of area of L3 band divided by total band area. Total AFP level was measured by enzyme immunoassay (Roche Diagnostics, Basel). The serum concentration of total AFP in IU/ml was converted to ng/ml by the factor of 1.25 according to manufacturer's recommendation. This study was not designed to determine the optimal cut-off values of either AFP-L3% or total AFP. Therefore, the cut-off value of AFP-L3 was set at 15% in accordance with the recommendation of a previous report[21] and a generally accepted cut-off value of 200 ng/ml and 400 ng/ml for total AFP was used for analysis.

Statistical analysis

Continuous variables were presented as mean ± standard deviation and compared using standard parametric and nonparametric methods where appropriate. Frequency data were presented as number and percentage and compared using the Chi-square test or Fisher's exact test where appropriate. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were obtained for each testing method based on the binomial distribution. All statistical testing was done at the conventional 2-tailed α level of 0.05.

Results

Patient characteristics

The main clinical and laboratory data gathered during the first visit to our institution are summarized in Table 1. The most common presenting symptoms and signs were upper abdominal pain, loss of appetite, and abdominal mass or in combination. Fever was found in one quarter of the patients. Eleven patients (11%) had signs of portal hypertension with ascites. Only three patients (3%) developed jaundice. However, there was no significant difference in the clinical presentation between patients with HCC and non-HCC. Of the entire population, the prevalence of HBV

Table 1. Clinical and laboratory features of the patient population and comparison between patients with HCC and those with non-HCC

	HCC group (n = 61)	Non-HCC group (n = 35)	p-value
Signs and symptoms; n (%)			
Abdominal pain	48 (79)	30 (86)	NS
Loss of appetite	50 (83)	22 (63)	NS
Abdominal mass	31 (51)	30 (86)	NS
Fever	14 (23)	10 (29)	NS
Ascites	6 (10)	5 (14)	NS
Jaundice	2 (2)	1 (3)	NS
Liver biochemistries			
Aspartate aminotransferase (U/L)	133 ± 103	121 ± 291	NS
Alanine aminotransferase (U/L)	90 ± 65	59 ± 38	NS
Alkaline phosphatase (U/L)	310 ± 292	315 ± 231	NS
γ-glutamyl transpeptidase (U/L)	342 ± 320	334 ± 278	NS
Total bilirubin (mg/dL)	1.2 ± 1.1	0.9 ± 0.7	NS
Albumin (g/dL)	3.9 ± 0.7	3.8 ± 0.5	NS
Haematologic indices			
Hemoglobin (g/dL)	39.6 ± 7.4	35.5 ± 6.0	NS
Platelet (x 1, 000/μL)	276 ± 156	311 ± 133	NS
Virologic markers (%)			
Hepatitis B surface antigen	72%	25%	NS
Anti-HCV antibodies	15%	22%	NS

Data are expressed as mean ± standard deviation. NS: not significant

The normal ranges are follows: aspartate aminotransferase, 0-37 U/L; alanine aminotransferase, 0-40 U/L; alkaline phosphatase, 39-117 U/L; γ-glutamyl transpeptidase, 7-50 U/L; total bilirubin, 0.3-1.2 mg/dL; albumin, 3.5- 5.5 g/dL

and HCV infection were 72%, and 15%, respectively. Patients with HCC had significantly a higher prevalence of viral hepatitis infection compared to patients with non-HCC. Liver enzymes and hematologic indices were similar between patients with HCC and non-HCC.

Demographic, biochemical, and histological characteristics of patients with HCC

The main clinical and biochemical data of patients with HCC was summarized in Table 2. The patient population with HCC was comprised of 50 males and 11 females, with a mean age of 48.8 years. According to the Okuda system, 3 patients were classed as stage I, 35 patients belonged to stages II, and 6 patients were classified in stage III. Thirty patients had single liver mass, 17 patients had more than one nodule, and 11 patients had diffuse infiltrative lesions. An AFP-L3% more than 15% was present in 82% (50/61) of the patients with HCC. Of these 50 patients with AFP-L3%, more than 15% differed from the rest of the patients in that they presented with significantly higher KPS scores ($p = 0.02$) and a higher elevation of serum alkaline phosphatase ($p = 0.04$). Hepatitis B surface antigen was detected in more than two-thirds of both groups whereas hepatitis C infection was only detected in patients with AFP-L3% of more than 15%. Otherwise, the 2 groups of patients did not differ significantly in term of age, sex, liver biochemistry values, tumor number, or tumor stage and histological features of the tumor according to the Edmondson grading system.

Operative characteristics of AFP-L3% and total AFP

The operative characteristics of both AFP-L3% and total AFP are described in Table 3. With the recommended AFP-L3% at a cut-off value of 15%, the sensitivity of the AFP-L3% for diagnosis of HCC was 82% (95% confidence interval [CI], 74-88), the specificity was 71% (95% CI, 58-82), the PPV was 83% (95% CI, 75-90), and the NPV was 69% (95% CI, 56-80). The majority (94%) of the 39 patients with total AFP higher than 200 ng/ml had HCC. Twenty-four (42%) of

Table 2. Demographics, and laboratory features of the 61 HCC patient and comparison between patients with AFP-L3% more than 15% and those with AFP-L3% less than 15%

	AFP-L3% ≥ 15% (n = 50)	AFP-L3% < 15% (n = 11)	p-value
Mean age; year	48	51	NS
Sex; F/M	9/41	2/9	NS
KPS; mean score	75	70	0.04
Liver biochemistries; mean value			
Aspartate aminotransferase (U/L)	135	127	NS
Alanine aminotransferase (U/L)	94	72	NS
Alkaline phosphatase (U/L)	334	208	0.02
γ-glutamyl transpeptidase (U/L)	359	267	NS
Total bilirubin (mg/dL)	1.2	1.3	NS
Albumin (g/dL)	3.9	3.8	NS
Virologic markers (%)			
Hepatitis B surface antigen	74%	66%	NS
Anti-HCV antibodies	19%	0	NS
Okuda staging (%)			
Stage I	7%	0	NS
Stage II	82%	90%	NS
Stage III	11%	10%	NS
Tumor number			
Single lesion	55%	33%	NS
2-3 lesions	19%	11%	NS
>3 lesions	12%	11%	NS
Diffuse infiltrative lesion	14%	45%	NS

KPS; Karnofsky performance status, NS: not significant

The normal ranges are follows: aspartate aminotransferase, 0-37 U/L; alanine aminotransferase, 0-40 U/L; alkaline phosphatase, 39-117 U/L; γ-glutamyl transpeptidase, 7-50 U/L; total bilirubin, 0.3-1.2 mg/dL; albumin, 3.5- 5.5 g/dL

Table 3. Tumor histologic features of the 61 HCC patients and comparison between patients with AFP-L3% more than 15% and those with AFP-L3% less than 15%

	AFP-L3% ≥ 15% (n = 50)	AFP-L3% < 15% (n = 11)	p-value
Trabecular pattern of tumor (%)			
Macrotrabecular	14%	18%	NS
Microtrabecular	86%	82%	NS
Cell type (%)			
Hepatic	94%	82%	NS
Clear	2%	0	NS
Mixed	4%	18%	NS
Edmondson grading (%)			
Grade I	0	0	NS
Grade II	49%	55%	NS
Grade III	49%	45%	NS
Grade IV	2%	0	NS63

NS; not significant

Table 4. Operative characteristics of AFP-L3% and different cut-off values of total AFP for the diagnosis of HCC

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Total AFP > 200 ng/mL in the entire population	61%	94%	95%	58%
Total AFP > 400 ng/mL in the entire population	56%	94%	94%	55%
AFP-L3% in the entire population	82%	71%	83%	69%
AFP-L3% in patients with total AFP < 200 ng/ml	83%	71%	67%	86%
AFP-L3% in patients with total AFP < 400 ng/ml	85%	71%	70%	86%

the 57 patients with total AFP less than 200 ng/ml had HCC, and the remaining 33 (58%) had non-HCC. In this subset of patients, an AFP-L3% of more than 15% was present in 83% of patients with HCC versus 29% of patients with non-HCC. With the recommended AFP-L3% at a cut-off value of 15%, the sensitivity and specificity of the AFP-L3% for diagnosis of HCC was maintained at 83% and 71%, respectively, the PPV decreased moderately to 67%, and the NPV increased moderately to 86%. Thus, in this subset of patients with a total AFP less than 200 ng/ml, ALP-L3% of more than 15% increased the confidence level in excluding the diagnosis of HCC while it maintained the sensitivity for detecting this cancer.

Discussion

Mortality rates for HCC have increased worldwide and in Thailand during the past two decades. Serum AFP has been routinely used as a biomarker for diagnosing HCC. However, diagnostic potential of this marker to differentiate HCC from other malignant liver tumors is poor. This has led to increased interest in identifying tumor markers with greater clinical utility. AFP-L3%, the *Lens culinaris* agglutinin-reactive fraction of AFP, has been reported to be more specific marker for the diagnosis of HCC than total AFP level[11]. It has been widely used for early recognition of HCC[14,15] and prognostic indicator after treatment in Japan[12,13]. In the present study, AFP-L3% at a cut-off point of more than 15% provided sensitivity of 82% and specificity of 71% in the diagnosis of HCC. These results were similar or slightly lower when compared to those of previous studies, which have shown sensitivities and specificities ranging from 36% to 96% and 89% to 94%, respectively[21-26]. The difference in the results among these studies may derive from the following factors. First, in the present study, ALP-L3% was evaluated only in cancer patients who present with symptomatic liver mass compared to other malignant liver cancer whereas previous case-control studies mostly used benign liver disease as the comparing group. Second, the present

study was not designed to determine the optimal cut-off values of both AFP-L3% and total AFP in the diagnosis of HCC; values used were taken from the literature, and from the manufacturer (for AFP-L3%). A recent study suggested that a cut-off value for AFP-L3% of 35% had a specificity of 100% in those with a total AFP of 10-200 ng/ml[15]. However, increasing in the specificity was associated with decreased sensitivity from 71% to 33%. Therefore, our study using a different cut-off value from other studies may have differed in the results. Lastly, considering that AFP is often elevated in chronic hepatitis B or C infection, underlying chronic hepatitis may have affected the test properties of AFP-L3% in the present study. However, our study demonstrated that increased aminotransferase was not associated with positivity for AFP-L3%.

Previous studies have suggested that positivity for AFP-L3% may be an unfavorable prognostic factor in patients with HCC[12-15]. Oka and colleagues have reported that the characteristics of an advanced tumor including the number of tumors, maximum diameter, tumor spread, portal vein invasion, tumor stage, and tumor classification, were associated with a positive AFP-L3% (cut-off value at 10%) in HCC patients[27]. In the present study, we observed no association between the positivity of AFP-L3% (cut-off value at 15%) and the number of tumor, tumor stage or histological grade. This is consistent with the results from other groups[28-30]. This discrepancy may be, in part, due to difference in the underlying etiology and tumor biology in these studies. Furthermore, the fluctuation in levels of AFP-L3 could occur over time and would diminish the clinical utility of any single value. Therefore, a single elevated or normal value may need to be repeated and caution in interpreting a single abnormal test is advised. Another explanation was that there should have been another selection bias on the patient enrollment in the present study. This is because the inclusion of participants was limited only to patients who have pathological confirmation of cancer and the majority of our patients had Okuda tumor stage II. The more advanced disease stage is not suitable for a liver biopsy and is automatically excluded from the study.

In conclusion, although the measurement of AFP-L3 provides high sensitivity in the diagnosis of HCC, it has lower specificity and PPV for confirmation of the diagnosis of HCC than the determination of total AFP in individuals who present with symptomatic liver mass. However, when considering high NPV of AFP-L3 in patients with AFP < 200 ng/ml, this may be useful as an adjunctive marker, in combination with AFP, to aid in the exclusion of a diagnosis of HCC.

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ประโยชน์ทางคลินิกของ *Lens culinaris agglutinin-reactive alpha-fetoprotein* ในการวินิจฉัยมะเร็งตับ *hepatocellular carcinoma* ในโรงพยาบาลขนาดใหญ่ที่รับส่งต่อผู้ป่วย

ทวีศักดิ์ แทนวันดี, สุภัทศรี เศรษฐสินธุ์, พูลชัย จรัสเจริญวิทยา, ศิวะพร ไชยนุวัติ, สมชาย ลีลากุศลวงศ์, นนทลี เผ่าสวัสดิ์, วิจิตร ศรีกุเรชา, สุพจน์ พงศ์ประสบชัย, สถาพร มานัสสถิตย์, อุดม คชินทร, ปัทมา เอกโพธิ์, ศันสนีย์ เสนะวงษ์

ภูมิหลังและวัตถุประสงค์: *ในปัจจุบันยังไม่ทราบบทบาททางคลินิกของ Lens culinaris agglutinin-reactive alpha-fetoprotein (AFP-L3%) ในการดูแลผู้ป่วยมะเร็งตับ hepatocellular carcinoma (HCC) ในผู้ป่วยไทย การศึกษานี้เป็นการศึกษาประโยชน์ของ AFP-L3% ในการวินิจฉัย HCC ในผู้ป่วยไทยในโรงพยาบาลขนาดใหญ่ที่รับส่งต่อผู้ป่วย*

วัสดุและวิธีการ: *ได้ทำการศึกษาในผู้ป่วยที่ได้รับการวินิจฉัยโดยพยาธิวิทยาว่าเป็นมะเร็งตับชนิด HCC จำนวน 61 ราย และผู้ป่วยที่เป็นมะเร็งตับชนิดอื่นอีก 35 ราย*

ผลการศึกษา: *ผู้ป่วย HCC จำนวน 61 รายประกอบด้วยชาย 50 ราย หญิง 11 ราย อายุเฉลี่ย 48.8 ปี โดยผู้ป่วยอยู่ในระยะที่ 1จำนวน 3 ราย ระยะที่ 2 จำนวน 35 ราย และระยะที่ 3 จำนวน 6 ราย ตามระบบของ Okuda พบว่าเมื่อใช้ระดับของ AFP-L3% ที่มากกว่าร้อยละ 15 จะมีความไวในการวินิจฉัย HCC เท่ากับร้อยละ 82 และมีความจำเพาะ ร้อยละ 71 โดยมี positive predictive value ร้อยละ 83 และ negative predictive value ร้อยละ 69 ในการวินิจฉัย HCC สำหรับผู้ป่วย HCC ที่มีระดับ AFP น้อยกว่า 200 ng/ml การใช้ระดับ AFP-L3% ที่มากกว่าร้อยละ 15 ไม่เพียงแต่ทำให้มีความไวในการวินิจฉัยสูงถึงร้อยละ 83 ยังมีความจำเพาะที่ดี คือร้อยละ 71 และยังพบว่า negative predictive value ยังสูงถึงร้อยละ 86*

สรุป: *AFP-L3% มีความไวสูงในการวินิจฉัย HCC แม้จะมีความจำเพาะน้อยกว่าระดับ AFP ในการวินิจฉัยผู้ป่วยที่มีก้อนในตับ อย่างไรก็ตามเมื่อคำนึงถึง NPV ที่สูงโดยเฉพาะในผู้ป่วยที่มีระดับ AFP น้อยกว่า 200 ng/ml การใช้ AFP-L3% ก็น่าจะมีประโยชน์ทั้งโดยตรง หรือ ร่วมกับ AFP ในการใช้วินิจฉัยผู้ป่วย HCC*