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Original Article

Evaluation of GALAD Score in Diagnosis and Follow-up of Hepatocellular Carcinoma after Local Ablative Therapy

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Abstract

Background and Aims: Strategies for detection of early hepatocellular carcinoma (HCC) are still limited. The GALAD score is a serum biomarker-based model designed to predict the probability of having HCC. We aimed to assess the ability of GALAD score to diagnose early HCC and its validity to follow patients after local ablation therapy. ***Methods:*** This multicenter prospective study included 108 patients in two groups, 58 HCC patients (67 focal lesions) with local ablative therapy (study group), and a control group of 50 patients with liver cirrhosis. The GALAD scores of the study and control groups, and of the HCC patients before and after ablative therapy were compared. ***Results:*** Most patients were men (74.1% in study group and 76% in controls) with hepatitis C virus infection (98.30% in the study group, and 94% in controls). GALAD scores were significantly higher in HCC patients than in those with benign cirrhosis (2.65 vs. −0.37, p=0.001). Ablative therapy was successful in 94.4% of focal lesions <2 cm, and in 86.10% of 2–5 cm lesions. The GALAD score was also significantly lower at 1 month after ablation in patients with well-ablated tumors (2.19 vs. 0.98, p=0.001). The best cutoff values of GALAD score for diagnosis of early HCC, and for prediction of well ablation of HCC were 0.74 and ≤3.31 (areas under the curve of 0.92 and 0.75, sensitivities of 84.48% and 76.19%, specificities of 89.13% and 83.33%, positive predictive values of 90.74% and 94.1%, and negative predictive values of 82% and 35.7% respectively). ***Conclusion:*** The GALAD score was effective for the diagnosis of early HCC and for follow-up after ablative therapy.

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Keywords: GALAD score; HCC; Ablative therapy; Liver cirrhosis; Egypt.

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CT, computed tomography; DCP, des-gamma-carboxy-prothrombin; HCC, Hepatocellular carcinoma; MRI, magnetic resonance imaging.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer worldwide and the second most frequent cause of cancer-related death. The incidence of liver cancer per 100,000 person-years is estimated as 9.3% and the mortality as 8.5%.[1] Egypt has a high incidence of HCC, which occurs in approximately 21% of patients with liver cirrhosis.[2] HCC was, until recently, diagnosed by histologic examination of tumor tissue. Now, it can be confirmed with high specificity from characteristic radiological features in tumors larger than 1 cm in diameter.[3] This approach avoids both the risk of bleeding and tumor seeding along the biopsy tract.[4,5] Surveillance is well accepted as key to effective delivery of potentially curative treatment. It involves ultrasound examination[6] followed by confirmatory tests to see if focal lesions are detectable. A 4-phase multidetector computed tomography (CT) scan or dynamic contrast-enhanced magnetic resonance imaging (MRI) are used with or without biopsy. The limitations of the radiological diagnosis of HCC are becoming increasingly recognized in the screening setting.[7]

The sensitivity of ultrasound for screening is usually between 65% and 80%, and is lower in early disease, in which appearances are not specific and the performance characteristics for surveillance in nodular cirrhotic livers are not well defined. It is also subjective, dependent on operator experience, and the available equipment.[8] Assay of serum alpha-fetoprotein (AFP) has also been used for diagnosis, with grossly elevated levels being highly specific for HCC,[9] but sensitivity is limited to 45% or less in smaller tumors.[6,10] Other diagnostic serological tests include des-gamma-carboxy-prothrombin (DCP), an abnormal prothrombin molecule derived from an acquired defect in the posttranslational carboxylation of the prothrombin precursor[11] and AFP-L3 (an isoform of AFP characterized by the presence of an alpha 1,6-linked residue on the AFP carbohydrate side chain.[12,13] However, none have alone proved to be a sufficient screening test.[14]

GALAD is a serum-based tool for the detection of HCC that was developed at a UK center using a statistical model that determined the risk of HCC in individual patients with chronic liver diseases. It is based on the objective measures of gender, age, and three serologic biomarkers, AFP, L3-AFP, and DCP.[15] All assays are commercially available

on a single standard platform.[16] The model has potential use for surveillance and may mitigate some of the limitations of ultrasound scanning, including reduced sensitivity in obese patients and patients with advanced cirrhosis. That is important for screening because the earlier the disease is detected, the better the chance of curative treatment. This study aimed to evaluate the ability of the GALAD score for early diagnosis of HCC and its ability to predict tumor course in HCC patients after ablative therapy.

Methods

This prospective cohort study was conducted from July 2017 to April 2019 in the gastroenterology and hepatology department of the Theodor Bilharz Research Institute, the hepatology and infectious disease department of the National Hepatology and Tropical Medicine Research Institute, and the hepatology unit of the Arab Contractors Medical Center. The study included 108 patients who were divided into two groups, 58 in the study group and 50 in the control group.

Inclusion criteria

The study group (58 patients) included adult Egyptian patients with HCC on top of liver cirrhosis (Child A or B) with a single focal lesion less than 5 cm in diameter or three lesions, each less than 3 cm in diameter, and no distant metastasis or vascular invasion. The diagnosis of HCC was established by triphasic CT contrast imaging and/or dynamic contrast-enhanced MRI. HCC was diagnosed if the lesion showed arterial enhancement and rapid wash-out in the portal and delayed phases.[17] The control group (50 patients) included patients with known liver cirrhosis with an absence of focal lesions on ultrasound screening. Patients with hepatic focal lesions other than HCC or late stages that would not benefit from curative therapies according to the Barcelona Clinic Liver Cancer (BCLC) criteria were excluded.

Included patients were subjected to a full medical history, clinical examination, laboratory investigations including a complete blood count, liver biochemical profile (bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, GGT, prothrombine time, INR, and serum albumin) and tumor markers including serum AFP, AFP L3, and DCP levels, and viral hepatitis markers (HCV Ab, HBsAg). Dynamic imaging modality, including triphasic CT, or dynamic MRI, was utilized to confirm the diagnosis of HCC if there is a focal lesion on abdominal ultrasound (US).

Calculation of the GALAD score

For all patient groups, the GALAD score was calculated as $Z = -10.08 + 0.09 \times \text{age} + 1.67 \times \text{sex} + 2.34 \times \log(\text{AFP}) + 0.04 \times \text{AFP-L3} + 1.33 \times \log(\text{DCP})$, where sex equals 1 for males and 0 for females.[15] The probability of HCC individual patients (ranging from 0 to 1) was estimated as $\Pr(\text{HCC}) = \exp(Z)/(1 + \exp(Z))$.[15] A follow-up GALAD score was calculated for patients who underwent ablative therapy after at least 1 month with a negative triphasic CT for tumor recurrence or acquisition of new focal lesions. Values of the GALAD score were compared between patients with HCC (study group) and the control group (patients with chronic liver disease and advanced fibrosis without HCC by imaging). In addition, values of the GALAD score were compared between patients with HCC before and 1 month after ablation.

Statistical analysis

Continuous values were reported as means ± standard deviation, or in the case of non-normally distributed data, as the median and interquartile range. Continuous data were analyzed using independent-sample *t*-tests or Mann–Whitney U tests in the case of skewed data. Chi-squared tests was used to compare the frequency of occurrence between different groups of patients. Paired samples were analyzed using a paired *t*-test or the Wilcoxon signed-rank test, according to normality. Pearson's or Spearman's correlation analysis was performed between the tumor characteristics (the number of lesions and the size of the tumor), patient characteristics, such as age, sex, performance status, or liver condition, and the GALAD score. Receiver operating characteristic (ROC) curve analysis was performed to identify the best cutoff value of the GALAD score, with maximum sensitivity and specificity for differentiation of cirrhotic patients with HCC from those without HCC.

Results

The study included 108 patients with chronic HCV divided into two groups (58 in the study group and 50 in the control group) in the period from July 2017 to April 2019. The study group (58) included patients with HCC on top of liver cirrhosis (Child A or B) with a single focal lesion of less than 5 cm in diameter or three lesions, each less than 3 cm in diameter, and no distant metastasis or vascular invasion. The control group (50 patients) included patients with known liver cirrhosis with an absence of focal lesions on US screening. No significant differences were found between both groups with regard to demographic features. Most patients in each group were men, 43 (74.10%) in the study group and 38 (76%) in the control group. Most resided in urban areas (65.50% and 72%) and were infected with HCV (98.30% and 94 %). Comparison of baseline laboratory data between both groups revealed significantly higher AFP, AFP-L3, hemoglobin, platelets, and albumin levels in patients with HCC, and significantly lower bilirubin level and INR values compared with the control group (Table 1). Comparison of the GALAD score between the two groups revealed significantly higher scores in patients with HCC compared with the control group (Table 1). Most patients (73.10%) had a single focal lesion that most often occurred in the right lobe (85.10%) and ranged from 2–5 cm (68.70%). No significant difference was found in the GALAD score between lesions less than or more than 2 cm. The median GALAD scores were 2.36 for lesions >2 cm in size and 2.64 for those <2 cm in size, p=0.813).

Most patients with HCC were Child A (49/58), most underwent radiofrequency ablation (44 patients (75.90%), and a microwave procedure was done for 14 (24.10%). Follow-up laboratory and imaging data for HCC cases at 1 month after ablation included 48/58 patients with 54 focal lesions, owing to the absence of the follow-up data of 10 patients who failed to appear in the follow-up period and because of technical problems and invalid samples. Most focal lesions were well ablated on follow-up CT at 1 month after ablation (88.80%). Lesions less than 2 cm in diameter had a higher ablation rate than lesions larger than 2 cm (94.40% vs 86.10%). ROC curves were performed to determine the best cutoff value of the GALAD score for the diagnosis of early HCC, which was 0.74 with an AUC of 0.92, sensitivity of 84.48%, specificity of 89.13%, positive predictive value of 90.74%, and negative predictive value of 82% (Fig. 1. and Table 2). We reviewed different GALAD score cutoffs and their corresponding sensitivities and specificities in previously published studies and tested the cut-

Table 1. Baseline laboratory data and GALAD scores of both groups

Baseline		Patient group (*n*=58)	Control group (*n*=50)	*p*-value
Hemoglobin, gm/dL	Mean	13	10.2	0.001
Total leucocyte count, /mm^3	Mean	5.50	5	0.207
Platelet count, /mm^3	Median	125	80	0.001
Albumin, gm/dL	Mean	3.60	2.40	0.001
Total bilirubin, mg/dL	Mean	1	2.3	0.001
INR	Mean	1.10	1.50	0.001
AST, IU/L	Median	36	42	0.707
ALT, IU/L	Median	31	22	0.001
Alkaline phosphatase, IU/L	Mean	105	108	0.618
Creatinine, mg/dL	Mean	0.90	1.20	0.001
AFP, ng/mL	Median	27.50	3.30	0.001
AFP-L3, %	Median	8.20	5.80	0.021
DCP, ng/mL	Median	14.7	14	0.213
GALAD score	Median	2.56	−0.37	0.001

AFP, Alfa feto protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCP, des-gamma-carboxy-prothrombin; INR, international normalization ratio.

offs in our cohort in a trial to reach the best possible cutoff that could be applied in different patient populations. The results of GALAD score cutoffs in previous studies and their corresponding sensitivities and specificities, together with results of these cutoffs on our cohort from sensitivity and specificity points of view are shown in (Table 3).[15,18–21]

GALAD scores were significantly lower at 1 month after ablation compared with the baseline value (1.32 vs. 2.37). The same applied to AFP and DCP. Albumin was significantly lower after ablation. Total bilirubin and INR were significantly higher than the baseline value. HB, leucocytes, and platelet counts were significantly lower after ablation. No significant differences in baseline demographic and virologic data and Child scores were found between patients with well-ablated versus partially ablated tumors (Tables 4, 5). The median GALAD score was significantly lower at 1 month after ablation in patients with well-ablated tumors compared with baseline (0.98 vs. 2.19, p=0.001). Similarly, GALAD scores and AFP values 1 month after ablation were significantly lower in patients with well-ablated lesions compared with those with partially ablated lesions. The median GALAD score was 0.98 in patients with well-ablated lesions, 3.90 in those with partially ablated lesions (p=0.001), and median AFP values were significantly lower for well-ablated lesions (13 ng/mL) compared with partially ablated lesions (151.50 ng/mL), p=0.02). Median GALAD scores were higher at 1 month after ablation than at baseline in patients with partially ablated tumors, but the difference was not significant (2.60 vs. 3.90, p=0.514). The ROC curve was measured to determine the cutoff value of GALAD score for the prediction of well-ablated HCC, and was found to be ≤3.31 with an AUC of 0.75, a sensitivity of 76.19%, a specificity of 83.33%, a positive predictive value of 94.10%, and a negative predictive value of 35.70% (Fig. 2).

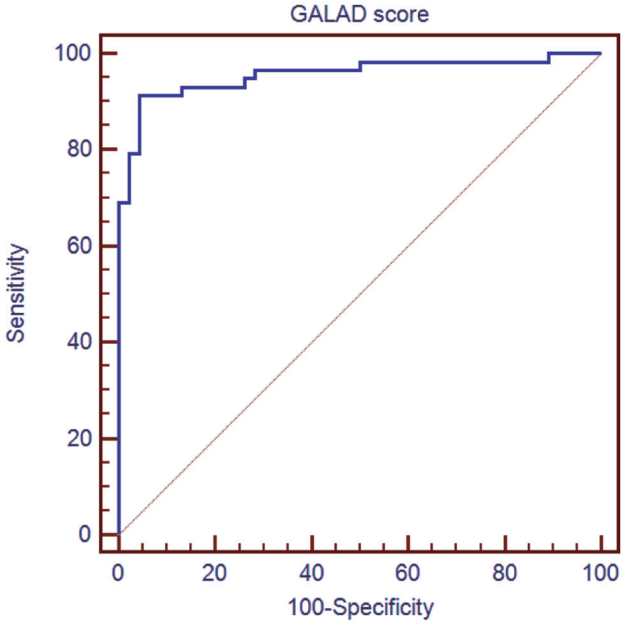

Fig. 1. Receiver operating characteristic curve of GALAD score as a predictor of hepatocellular carcinoma.

Discussion

The study aim was to assess the effectiveness of the GALAD score for the diagnosis of early HCC and the follow-up of HCC cases after ablative therapy. Our study results revealed that the GALAD score was significantly higher in cases with HCC than in those without HCC (2.56 vs. 0.37). This is consistent with Best *et al*.[18] who conducted a multicenter study of early HCC in an international cohort of patients with nonalcoholic steatohepatitis. They found significantly higher GALAD scores in patients with HCC than in those with benign cirrhotic livers (2.93 vs. −3.96) in German centers. However, the median GALAD score in the Japanese center in the same study was lower in patients with HCC vs. benign cirrhotic liver (−0.30 vs, −3.24), which may have been caused by low values of tumor markers integrated into the GALAD score, especially DCP, in those patients**.** In addition, Yang *et al*.,[19] who evaluated the GALAD score for HCC detection compared with liver US and the GALADUS score, reported that the median

Table 2. Predictivity of GALAD score for Early HCC

Parameter	AUC	Cutoff point	Sensitivity (%)	Specificity (%)	PPV	NPV
GALAD score	0.922	>0.74	84.50	89.10	90.70	82

Table 3. GALAD score cutoffs, corresponding sensitivities, and specificities in previously published studies and the resultant sensitivity and specificity of testing each cutoff in our cohort

Study		Number of HCC patients	Number of Non-HCC patients	Mean GALAD score cutoff	Sensitivity (%)	Specificity (%)	Early HCC cases (*n*)	Sensitivity (%)	Specificity (%)	Applying the studied cutoffs on our cohort	
										Sensitivity (%)	Specificity (%)
Johnson *et al*., 2014[15]		331	339	−36.0	98		61	75		98.28	57
				−63.1	98		61	85		98.28	10.8
				0.88	86		61	56		79.3	95.4
Best *et al*., 2016[20]		285	402	−36.0	85.6	93.3	61	68.3		98.28	57
Best *et al*., 2020[18]		125	231	−33.1	91.2	90.9	25	86.2	90.9	98.28	10.8
Best *et al*., 2020[18]				−36.0	84.4	95.2	25	68	95.2	98.28	57
Yang *et al*., 2019[19] (single center cohort)		111	180	−67.0	91	85	60	92	79	98.28	50
				−81.1	89	81				98.28	16
				−36.0	89	86	60	82	86	98.28	57
Yang *et al*., 2019[19] (multicenter cohort) Early Detection Research Network phase II		233	412	−71.0	76	86				96.55	71.7
				−36.0	79	79				98.28	57
Schotten *et al*., 2021[21]	Total	196	377				70				
	HBV	52	130	−36.0	76.9	95.4	18			98.28	57
	HCV	84	139	−36.0	89.7	95.7	42			98.28	57
	Other etiology	60	108	−36.0	89.3	95.7	10			98.28	57

Table 4. Comparison of laboratory data and GALAD score before and after ablation in the patient groups (*n*=48)

Laboratory		Baseline	Follow-up	*p*-value
HB (gm/dL)	Mean	13.10	12.60	0.001
TLC (/mm3)	Mean	5.60	4.80	0.001
PLT (/mm3)	Median	128	115	0.001
Albumin (gm/dL)	Mean	3.70	3.50	0.003
Total bilirubin (mg/dL)	Mean	1	1.20	0.029
INR	Mean	1.1	1.20	0.001
AST (IU/L)	Median	36	35	0.052
ALT (IU/L)	Median	30	32	0.068
ALP (IU/L)	Mean	106	103.60	0.473
Creatinine (mg/dL)	Mean	0.87	0.92	0.312
AFP (ng/mL)	Median	25.50	17	0.001
AFP-L3 (%)	Median	7.40	7.20	0.792
DCP (ng/mL)	Median	13.70	10	0.023
GALAD score	Median	2.37	1.32	0.001

AFP, Alfa feto protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCP, des-gamma-carboxy-prothrombin; Hb, hemoglobin; INR, international normalization ratio; PLT, platelets; TLC, total leucocytic count.

Table 5. Comparison of baseline laboratory data and GALAD score between patients with well-ablated and partially ablated tumors

Baseline		Well ablated, *n*=42	Partially ablated, *n*=6	*p*-value
HB (gm/dL)	Mean	13.10	13.10	0.690
TLC (/mm3)	Mean	5.70	4.60	0.476
PLT (/mm3)	Median	131.50	124.50	0.842
Albumin (gm/dL)	Mean	3.70	3.60	0.486
Total bilirubin (mg/dL)	Mean	1	0.95	0.574
INR	Mean	1.20	1.10	0.795
AST (IU/L)	Median	36	38.50	0.883
ALT (IU/L)	Median	30	38.50	0.440
ALP (IU/L)	Mean	105.60	99.10	0.467
Creatinine (mg/dL)	Mean	0.90	0.86	0.420
AFP (ng/mL)	Median	22.80	135.10	0.098
AFP-L3 (%)	Median	7.10	8.70	0.659
DCP (ng/mL)	Median	14	6.70	0.131
GALAD score	Median	2.19	2.60	0.541

AFP, Alfa feto protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCP, des-gamma-carboxy-prothrombin; Hb, hemoglobin; INR, international normalization ratio; PLT, platelets; TLC, total leucocytic count.

GALAD score in patients with HCC (3.80) was significantly higher than in patients without HCC (−2.60).

In this study, the best cutoff of the GALAD score for the detection of early HCC was 0.74, with a sensitivity of 84.40%, a specificity of 89.10%, an NPV of 82%, and a PPV of 90.74%. We reviewed different GALAD score cutoffs and their corresponding sensitivities and specificities in previously published studies[15,18–21] and tested the cutoffs in our cohort in a trial to reach the best possible cutoff that could be used in different patient populations. However, despite showing very high sensitivity when applying the different cutoffs (most more than 98%), the specificity results were unacceptable (most less than 60%) and carry the risk of high false positive results if used as a screening test. Despite having a high specificity (98.4%) when applying the cutoff proposed by Johnson *et al*.,[15] (0.88), the sensitivity was still less than that of our proposed cutoff (79.3 vs. 84.4%). The difference in the cutoffs between the studies and the higher cutoff in our study can be attributed to several factors related to the structure of the score itself which included age, sex, levels of AFP, AFP-L3, and DCP as core components. In our study, most cases were men (74%). Ahn *et al*.,[22] in a study of the association of serum tumor biomarkers with integrated genomic and clinical characteristics of HCC, found that serum biomarker levels differed with genetic variants and gene expression profiles in HCC, not only the clinical characteristics and tumor stage, may also have been related to the underlying etiology of liver disease. In our study, most patients had post-HCV CLD (98%). The findings highlight the importance of studying the GALAD score in different ethnic groups and among different etiologies of chronic liver disease to reach a standard reference for HCC disease among the spectrum of presentations. With regard to baseline tumor markers, our HCC patients showed highly significant AFP and AFP-L3 values compared with the control group, with no significant difference in the DCP values between groups. The results matched those of Best *et al*.,[18] in a Japanese study. In contrast, Yang *et al*.,[19] and Johnson *et al*.,[15] reported significant differences in AFP, AFP-L3, and DCP between the two groups.

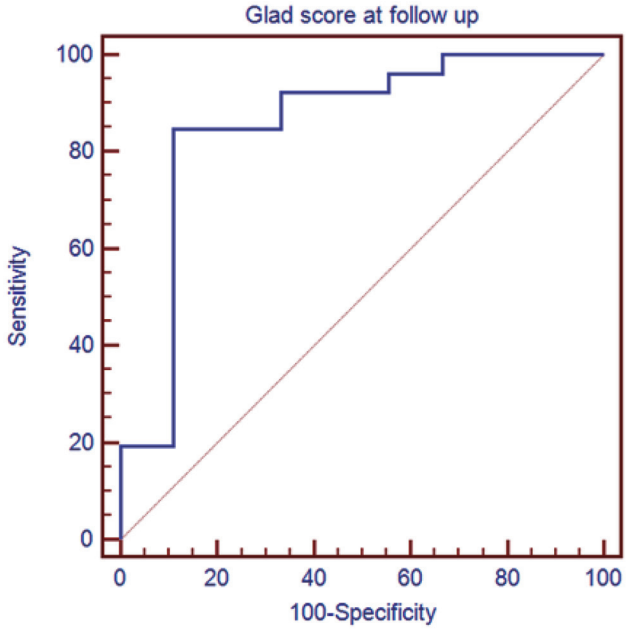

Fig. 2. Receiver operating characteristic curve curve of GALAD score as predictor of response in patients with well-ablated tumors.

To the best of our knowledge, our study is the first to assess the ability of the GALAD score to predict the course and response to therapy in HCC cases after ablative therapy. Our results revealed that the follow-up GALAD scores 1 month after ablation in patients who had well-ablated tumors were significantly lower than the baseline values, 2.19 before ablation vs. 0.98 after, a more than two-fold decrease. The best cutoff for the prediction of good ablation was ≤3.31, with an AUC of 0.75, a sensitivity of 76.10%, and a specificity of 83.33%. In contrast, the GALAD scores in patients with a partial response or tumor progression 1 month after ablation were higher but not significantly different.

In our study, most the patients underwent radiofrequency ablation (75.90%) and the rest (24.10%) underwent

microwave ablation following with the BCLC guidelines for the management of HCC.[23] With regard to the efficacy of ablation for focal lesions, most lesions showed a complete response (94.40% in lesions <2 cm and 86.10% for lesions from 2–5 cm). That agrees with Abdelaziz *et al*.,[24] who studied efficacy and survival of achieved with percutaneous radiofrequency compared with microwave ablation in HCC. They reported that most focal lesions had a complete response (96.50% in lesions <3 cm in diameter and 92.68% in lesions 3–5 cm) by either technique. The difference was not significant. In our study, most patients had a single focal lesion, mainly in the right lobe of the liver. That is in line with the findings of Amoros *et al*.,[25] and Kamal *et al*.[26] With regard to the socio-demographic characteristics of the study patients, most were men (74% in the HCC group and 76% in the cirrhosis group), and the patients with HCC were older than those in the cirrhotic group, but the difference was not significant. The finding was in accordance with studies conducted by Choi *et al*.[22] and Amoros *et al*.[27]

Regarding baseline laboratory data and Child–Pugh classification, the patients with HCC had increased albumin and normal bilirubin levels, nearly normal prothrombin time, and were more likely to be Child–Pugh class A compared with the control group. The better liver biochemical profile might be explained by the selection bias of well-compensated HCC cases to allow for therapeutic intervention, and consistent with the findings of Johnson *et al*.,[15] Soliman *et al*.,[18] and Best *et al*.[28]

Our study has several strengths. The most important is the study of cases with early-stage tumors, where 31.30% of the included focal lesions were less than 2 cm in diameter with curative potential. The main value of surveillance is to detect potentially curative disease. The median GALAD score in patients with focal lesions less than 2 cm was 2.64, which was significant for the diagnosis of early HCC, and as mentioned above, a cutoff score of 0.74 had excellent sensitivity, specificity, NPV, and PPV for the prediction of HCC. It was thus, a good tool for screening HCC, overcame the low sensitivity of US and AFP alone, and avoided radiation exposure, invasiveness, and the cost of other radiological modalities.

The data will help us to use the GALAD score for follow-up after ablative procedures. Further studies in larger numbers of patients will validate the best cutoff value to achieve cure and reduce the need for radiological modalities such as triphasic CT and dynamic MRI, which would decrease multiple radiation exposures, renal contrast insult, and patient cost.

Based on the study results, we can conclude that the GALAD score was clinically useful, rapid, and accurate for the diagnosis of early HCC and was a good prognostic tool, especially in patients with well-ablated focal lesions.

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None to declare.

Conflict of interest

ME has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Contributed to this paper with conception and design of the work (AS, RE, ME), collected patient data and attended clinical sessions (AA, MH), performed the literature review drafted the manuscript (RE, AS, ME), All authors participated in revising, editing, approving the final version of the manuscript.

Ethical statement

This work was conducted following the ethical principles of declaration of Helsinki. All patients gave their written an informed consent before enrollment. The study was approved by the Ethical Committee of Kasr Al-Aini School of Medicine in 2017 (Serial number: I-200316).

Data sharing statement

Data are available from the corresponding author on reasonable request.

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