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HCC-Mark: a simple non-invasive model based on routine parameters for predicting hepatitis C virus related hepatocellular carcinoma

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ABSTRACT

Background: Early detection of hepatocellular carcinoma (HCC) is crucial in providing more effective therapies. As routine laboratory variables are readily accessible, this study aimed to develop a simple non-invasive model for predicting hepatocellular cancer.

Methods: Two groups of patients were recruited: an estimation group (n = 300) and a validation group (n = 625). Each comprised two categories: hepatocellular cancer and liver cirrhosis. Logistic regression analyses and receiver operating characteristic (ROC) curves were used to develop and validate the HCC-Mark model comprising AFP, high-sensitivity C-reactive protein, albumin and platelet count. This model was tested in cancer patients classified by the Barcelona Clinic Liver Cancer (BCLC), Cancer of Liver Italian Program (CLIP) and Okuda systems, and was compared with other non-invasive models for predicting hepatocellular cancer.

Results: HCC-Mark produced a ROC AUC of 0.89 (95% CI 0.85–0.90) for discriminating hepatocellular carcinoma from liver cirrhosis in the estimation group and 0.90 (0.86–0.90) in the validation group (both $p < 0.0001$). This AUC exceeded all other models, that had AUCs from 0.41 to 0.81. AUCs of HCC-Mark for discriminating patients with a single focal lesion, absent macrovascular invasion, tumour size <2 cm, BCLC (0-A), CLIP (0–1) and Okuda (stage I) from cirrhotic patients were 0.88 (0.85–0.90), 0.87 (0.85–0.89), 0.89 (0.85–0.93), 0.87 (0.84–0.89), 0.85 (0.82–0.87) and 0.86 (0.83–0.89), respectively (all $p < 0.0001$).

Conclusion: HCC-Mark is an accurate and validated model for the detection of hepatocellular cancer and certain of its clinical features.

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KEYWORDS
HCC-Mark; hepatocellular carcinoma; routine parameters; early prediction; small tumour; HCC staging system

Introduction

Hepatocellular cancer is ranked as the sixth cancer and the second global cancer-related death, a leading cause being hepatitis C virus (HCV) infection [1,2]. Monitoring liver nodules and finding a tumour early are crucial in improving patient outcomes and in providing more effective therapies, which cannot be achieved in late diagnosis [1]. Hepatocellular cancer is more frequent in men than in women [3]. Screening for hepatocellular cancer is mainly based on clinical, laboratory and imaging tools. Despite performance limitations of alpha-fetoprotein (AFP) in the early stages, it remains the main diagnostic marker for hepatocellular cancer, although some patients are diagnosed with normal AFP which may remain during the entire course of the disease [4]. In addition, ultrasonography is limited by skill and experience of the operator, patient's constitution and cannot differentiate liver cirrhotic nodules from small hepatocellular cancers [4]. Ultrasound has a limited sensitivity (32–65%) for early-stage hepatocellular cancer [5] and 97% specificity [6].

Once hepatocellular cancer is diagnosed, staging is a chief part of prognosis and treatment [7]. As a result of the heterogeneous nature of hepatocellular cancer, combinations of routine haematology and biochemistry laboratory biomarkers can be superior to single biomarkers for diagnosis and staging [4,8]. An ideal marker for diagnosis would be non-invasive, accurate, accessible and inexpensive. A model based on routinely laboratory variables would meet these criteria [9].

The primary objective of our work was to develop and validate a simple model (HCC-Mark) based on routine laboratory markers for early hepatocellular cancer diagnosis from patients with liver cirrhosis and estimate its diagnostic performance in three internationally recognised hepatocellular cancer staging systems. The secondary objective was to evaluate the diagnostic performance of HCC-Mark model compared to common liver fibrosis and cirrhosis scores (Table 1) in the diagnosis of hepatocellular cancer.

Materials and methods

Between 2014 and 2017, a group of 300 consecutive patients with a diagnosis of cirrhosis or hepatocellular cancer for an estimation study and 625 patients

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Table 1. The formula of non-invasive models.

Author [Ref.]	Year	Model	Calculation
Tseng et al, [16]	2013	AARP	AAR/[platelet count (10^9/L)/150]
Zhu et al, [4]	2017	APAR	1000 × AFP (ng/ml)/(PLT(×10^9/L)×ALT (U/L)
Patel et al, [10]	2016	Fib4 + AFP	Fib-4 and AFP >20 (U/L)
Attallah et al, [32]	2012	FRT	3.31+ Age (years)×0.09+ APRI×1.5+ AFP (IU/ml)×0.4 – Alb (g/L)×0.14
Attallah et al, [33]	2013	BRC	(AST/ULN)/PLt (10^9/l) × 100
Attallah et al, [13]	2013	HCC-ART	2.17 + [log(AFP−1) × 10 × 0.117] + AAR × 0.025 + age × 0.012 + ALP (U/L) × 0.001] − [alb (g/L) × 0.015
Attallah et al, [34]	2017	Simplified HCC-ART	Age (years) × log AFP (U/L) × AAR × ALP (U/L)]/[Alb (g/L)
This study	2021	HCC-Mark	[AFP (U/L) x hs-CRP (mg/L)/(Alb (g/L) x PLT (×109/L))] x100

Abbreviations:
PLT = platelet; INR = international normalized ratio; AAR = aspartate aminotransferase/alanine aminotransferase; Alb = albumin; ALP = alkaline phosphatase; creat = cratinine; ULN = upper limit of normal; APAR = alpha fetoprotein, platelet and alanine aminotransferase ratio; FRT = fibrosis routine test; BRC = biotechnology research centre; HCC-ART = hepatocellular carcinoma-AFP-routine test

with cirrhosis or hepatocellular cancer diagnosis for a validation study were recruited into this prospective study. Patients in the validation study had the same clinical feature of that used in the estimation study to confirm the reproducibility of the applied model (HCC-Mark). They were recruited from Tropical Medicine Department, Mansoura University Hospitals, Mansoura, Egypt.

All patients had positive HCV-antibodies and were confirmed using HCV-RNA determination. Hepatocellular cancer was diagnosed using the American Association for the Study of Liver Disease (AASLD) guidelines [11]. Focal lesion size was defined using ultrasound, triphasic computed tomography (CT) or dynamic magnetic resonance imaging (MRI). All the hepatocellular cancer patients had no prior anti-cancer treatment such as hepatectomy, transarterial chemoembolization or radiofrequency ablation. Cirrhosis was diagnosed based on clinical, biochemical and ultrasonographic criteria [12] and followed up using regular ultrasound and AFP. Hepatocellular cancer was determined for surveillance program using AFP, ultrasound, or the combination.

All patients in this study were treatment naïve for HCV. Patients with hepatitis B, history of alcohol intake and other chronic liver disease were excluded. Patients with infectious disease, cardiovascular diseases, chronic kidney diseases, autoimmune diseases, metabolic disorders or other malignancies were excluded. All patients confirmed informed consent and well done in compliance with Institutional Research Board Mansoura Faculty of medicine and the ethical guidelines of the1975 Helsinki declaration.

Clinical data were collected and confirmed by imaging characteristics (ascites, focal lesion, tumour size and macrovascular invasion) to differentiate patients with cirrhosis from those with small and well-defined hepatocellular cancer. The Child–Pugh score was used to determine the degree of decompensation and classified as shown in Table 2. After diagnosis for every patient, laboratory investigation included liver function tests and high-sensitivity C-reactive protein (hs-CRP) were measured using an automated biochemistry analyser (BT1500; Biotecnica, S.P.A, Italy). Complete blood pictures were performed using an automated haematology analyser (Micros 60; Horiba medical, Montpellier, France). Prothrombin–INR was determined by (Coatron. M1; TECO, Neufahrn, Germany). AFP level and HCV antibody were estimated using an Immunofluorescence assay (IFA) by autoanalyzer (Mini-Vidas; bioMérieux, Paris, France). HCV-RNA was analysed by quantitative real-time polymerase chain reaction (COBAS Ampliprep/COBAS TaqMan; Roche Diagnostics, Pleasanton).

Continuous normally distributed data were expressed as mean and SD, whereas non-normally distributed variables were expressed as median and interquartile range (IQR). Statistically significant differences between groups were determined using chi-square test (x^2), the Student's t-test and Mann–Whitney U test. P-value < 0.05 was considered statistically significant. The endpoint was to identify patients with hepatocellular cancer from liver cirrhosis. Significant variables were entered in the multiple logistic regression analysis to develop a predictive simplified model that combined the independent factors without coefficients [13].

ROC curve was used to evaluate the diagnostic power of single markers and HCC-Mark model for discriminating hepatocellular cancer from patients with liver cirrhosis. Common indicators of the candidate blood markers and the model performance were calculated using standard formulae. Odds ratios (95% confidence interval) were calculated to assess the risk of a particular disorder. The calculation of routine models is presented in Table 1. Four routine laboratory blood test (4RLB) [14], the model for end-stage liver disease (MELD) [15], AAR-platelet score (AARP) [16], fibrosis index (FI) [17], fibrosis-cirrhosis index (FCI) [18], Fibro alpha [19] and platelet/age/phosphatase/AFP/AST index (PAPAS) [20] were also assessed. The diagnostic power of these routine models was validated and compared with HCC-Mark score.

Results

The laboratory and Child-Pugh data of patients are presented in Table 2. Both groups had more men, and those with cancer were older, but these metrics did not differ between the groups. Unsurprisingly,

Table 2. Laboratory data of patients with hepatocellular carcinoma and liver cirrhosis in estimation and validation groups.

	Estimation group (n=300)			Validation group (n=625)		
Variable	Cirrhosis (n=125)	HCC (n=175)	P value	Cirrhosis (n=245)	HCC (n=380)	P value
Gender						
Male %	73 (58.4%)	133(76%)	< 0.0001	141 (57.6%)	278(73.2%)	<0.0001
Female %	52 (41.6%)	42 (24%)		104 (42.4%)	102 (26.8%)	
Age (years)	56.8 ± 7.7	58.9 ± 7.2	0.041	56.0 ± 7.9	58.5 ± 6.9	0.024
Alanine aminotransferase (U/L)	39 (25 - 54)	53 (42 - 57)	0.037	40 (26 - 61)	53 (42 - 55)	0.004
aspartate aminotransferase (U/L)	55 (35 - 72)	64 (57 - 75)	0.007	56 (35 - 70)	64 (62 - 67)	0.01
Alkaline phosphatase (U/L)	134 ± 35	180 ± 65	0.005	133 ± 44	178 ± 89	0.002
Total bilirubin (μmol/L)	20 (14 - 31)	24 (15 - 36)	0.009	20 (14 -31)	22 (15 – 34)	0.012
Albumin (g/L)	34.5 ± 6.8	31.3 ± 5.6	< 0.0001	34.3 ± 6.8	31.9 ± 5.2	<0.0001
Prothrombin-INR	1.4 ± 0.3	1.3 ± 0.2	0.014	1.4 ± 0.3	1.3 ± 0.2	0.02
Creatinine (mg/dL)	0.99 ± 0.3	1.0 ± 0.2	0.256	0.97 ± 0.3	0.99 ± 0.3	0.182
Haemoglobin (g/L)	116 ± 22	122 ± 19	0.007	116 ± 21	120 ± 19	0.004
Total leucocytic count ($\times 10^9$/L)	5.5 ± 2.6	5.7 ± 2.9	0.53	5.5 ± 2.5	5.5 ± 2.8	0.885
Platelet count ($\times 10^9$/L)	106 (73 - 160)	98 (90 - 130)	< 0.0001	99 (69 - 150)	98 (78 - 132)	<0.0001
Quantitative HCV PCR (IU/ml)($\times 10^5$)	4.9 (1.2 – 13.5)	1.6 (0.7 - 7.5)	0.297	4.3 (1.2 – 15.6)	1.4 (0.3 - 7.1)	0.312
C-reactive protein (mg/L)	3.1 ± 0.17	10.9 ± 2.1	< 0.0001	3.5 ± 0.19	10.5 ± 1.7	<0.0001
α- Fetoprotein (U/L)	5.2 (3.2 - 9.3)	34 (9.1 - 331)	< 0.0001	3.4 (6.0 – 11.8)	32 (9.6 - 302)	<0.0001
Child Pugh A (n; %)	(68; 54.4%)	(93; 53.1%)	0.709	(130; 53.1%)	(208; 54.7%)	0.541
Child Pugh B (n; %)	(48; 38.4%)	(67; 38.3%)		(96; 39.2%)	(138; 36.3%)	
Child Pugh C (n; %)	(9; 7.2 %).	(15; 8.6 %)		(19; 7.7 %).	(34; 8.9 %)	

Normally distributed variables expressed as mean ± SD, non-normally distributed variables as median (IQR).

many indices differed between cirrhosis and cancer in both groups. The p values in the validation group were often smaller because of the greater sample size: numerical differences were roughly equivalent.

Using ROC curve analysis, the diagnostic powers of routine blood markers were used in order to differentiate hepatocellular cancer from liver cirrhosis: AUCs of the significant markers were AFP 0.79, hs-CRP 0.76, albumin 0.66 and platelets count 0.63 with (all $P < 0.0001$). At cut-off 400 U/L, the diagnostic accuracy of AFP was 46%, sensitivity 20% and specificity 100% with an odds ratio/95% CI of 1.25 (0.74-0.82) and $p < 0.0001$, whereas hs-CRP had high sensitivity and low specificity compared to AFP 72% and 70%; respectively with an odds ratio/955 CI of 5.84 (0.70-0.80) and $p < 0.0001$. The combination (AFP x hs-CRP) showed an AUC of 0.88, albumin and platelets count had 70% and 56% sensitivity, 62% and 54% specificity with an odds ratio/95% CI of 3.71 (0.61-0.72) and $p = 0.009$ and 1.47 (0.54-0.65) and $p = 0.01$, respectively.

The most discriminatory factors in univariate analysis were assessed by multiple logistic regression analysis. This regression was used to devise a simplified mathematical formula for discriminating patients with hepatocellular cancer from liver cirrhosis. This model, HCC-Mark, is defined as follows: [AFP (U/L) x hs-CRP (mg/L)/(Alb (g/L) x PLT ($\times 10^9$/L))] x100. The best combination was selected to achieve optimized diagnostic power with the highest AUC value.

The median of HCC-Mark in liver cirrhosis and hepatocellular cancer were 0.11 and 5.47; respectively. HCC-Mark model was applied for discriminating hepatocellular cancer from liver cirrhosis produced an AUC of 0.89 (0.85-0.90) and $p < 0.0001$. The optimal cut-off value of 0.5 was selected using ROC analysis. According to this cut-off, HCC-Mark had 82% sensitivity, 81% specificity and 81% accuracy for discriminating hepatocellular cancer patients from liver cirrhosis. HCC-Mark showed AUC 0.91 (0.88-0.94) and $p< 0.0001$ (with 82% sensitivity and 84% specificity) for discriminating patients with hepatocellular cancer from liver cirrhosis Child–Pugh A, 0.86 (0.83-0.89) and $p < 0.0001$ (with 82% sensitivity and 79% specificity) for Child–Pugh B and 0.82 (0.74-0.88) and $p < 0.0001$ (with 82% sensitivity and 67% specificity) for Child–Pugh C.

Having established the HCC-Mark in the estimation group, it was tested in a validation group for its ability to detect clinical variables and links with the international staging systems: BCLC [21], CLIP [22] and Okuda systems [23] (Table 3).

The combination (AFP x hs-CRP) showed an AUC of 0.86 (0.82-0.91) and $p < 0.0001$, whereas HCC-Mark (with albumin and platelet count added) yielded an AUC of 0.90 (0.88-0.92) and $p < 0.0001$. The diagnostic power of HCC-Mark was evaluated for discriminating patients with hepatocellular cancer from liver cirrhosis Child–Pugh A, B and C as presented in Table 3. AUCs of AFP x hs-CRP for discriminating early-stages of BCLC (0-A) was 0.80 (0.78-0.85) and $p < 0.0001$, CLIP (0–1) was 0.82 (0.79-0.86) and $p < 0.0001$ and Okuda (stage I) was 0.84 (0.80-0.89) and $p < 0.0001$. HCC-Mark showed higher AUCs for discriminating patients with only single focal lesions, absent macrovascular invasion, tumour size <2 cm and its values increase with hepatocellular cancer progression from early to advanced stages of hepatocellular cancer, although none of these were statistically significant. Moreover, AUCs of HCC-Mark were increased for discriminating early-stages in the three common staging systems BCLC, CLIP and Okuda from cirrhotic patients and its value increase in advanced tumour stages. The 95% CIs of the BCLC 0-A and C/D and the two CLIP stages failed to overlap, indicating a significant difference in the AUC and so discriminatory power.

Table 3. Diagnostic power of HCC-Mark to discriminate 380 patients with hepatocellular carcinoma from 245 patients with liver cirrhosis in the validation group.

Classification	HCC-Mark Median (IQR)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Liver cirrhosis Child–Pugh A (n= 130) vs. HCC	0.02 (0.07 - 0.15)	0.93 (0.89 - 0.95)	84	83	94	65	84
Liver cirrhosis Child–Pugh B and C (n= 96) vs. HCC	0.15 (0.52 - 2.04)	0.83 (0.81 - 0.89)	84	77	92	60	83
Total liver cirrhosis (n=245) vs. HCC	0.04 (0.14 - 0.59)	0.90 (0.88 - 0.92)	84	80	87	77	83
Number of nodules (n; %)							
Single (202; 53.2%)	0.11 (0.51 - 5.37)	0.88 (0.85 - 0.90)	84	80	78	86	82
Multiple (178; 46.8%)	0.15 (0.82 - 11.6)	0.89 (0.86 - 0.91)	85	80	76	88	82
Macrovascular invasion (n; %)							
Absent (331; 87.1%)	0.11 (0.62 - 5.79)	0.87 (0.85 - 0.89)	84	80	85	78	82
Present (49; 12.9%)	0.16 (0.76 - 67.21)	0.94 (0.90 - 0.96)	90	80	47	98	82
Size of nodules (n; %)							
< 2 (90; 23.7 %)	0.07 (0.17 - 1.15)	0.89 (0.85-0.93)	83	80	60	93	81
≥ 2 (290; 76.3 %)	0.15 (0.91 - 25.76)	0.88 (0.85-0.90)	85	80	83	82	83
BCLC stage (n; %)							
0–A (164; 43.2%)	0.36 (1.77-5.79)	0.87 (0.84 - 0.89)	82	80	73	87	81
B (137; 36.0%)	0.46 (2.7-18.24)	0.87 (0.84-0.90)	83	80	70	89	81
C and D (79; 20.8 %)	9.99 (87.65 - 728.49)	0.93 (0.90-0.95)	91	80	60	97	83
CLIP stage (n; %)							
0–1 (235; 61.8%)	0.38 (2.04 - 5.28)	0.85 (0.82 - 0.87)	82	80	80	82	81
≥ 2 (145; 38.2%)	2.76 (4.49 - 496.24)	0.94 (0.92 - 0.96)	86	80	72	90	82
Okuda stage (n; %)							
< 1 (199; 52.4%)	0.64 (3.13 - 36.03)	0.86 (0.83 - 0.89)	82	80	77	84	81
≥ 1 (181; 47.6%)	0.87 (11.6 - 321.27)	0.91 (0.88 - 0.93)	87	80	76	89	83

Abbreviations:
AUC = area under (ROC) curve; BCLC = Barcelona Clinic Liver Cancer; CLIP = Cancer of the Liver Italian Program; HCC = hepatocellular carcinoma; NPV = negative predictive value; PPV = positive predictive value; n = number.

Table 4. Diagnostic power of candidate models for prediction of HCC.

Marker	AUC (95% CI)	Cut-off	Diagnostic performances (%)					OR (95% CI)
			Sensitivity	Specificity	PPV	NPV	Accuracy	
APAR	0.75 (0.73 - 0.78)	1.85	75	57	73	60	68	3.99 (3.06 –5.21)
Fib4 + AFP	0.75 (0.76 - 0.82)	1.5	70	68	77	59	69	5.01 (3.82 – 6.57)
FRT	0.79 (0.77 - 0.82)	11.4	72	71	79	62	71	6.17 (4.67 - 8.14)
BRC	0.80 (0.77- 0.83)	14.1	76	70	80	65	73	7.37 (5.56 - 9.76)
HCC- ART	0.80 (0.78 - 0.83)	2.5	77	69	79	66	74	7.39 (5.59 – 9.78)
Simplified HCC-ART	0.81 (0.78 - 0.84)	280	81	64	78	68	74	7.36 (5.56 - 9.75)
HCC-Mark	0.90 (0.86 - 0.90)	0.5	84	78	87	77	83	18.72 (13.6 -25.7)

Abbreviations: AUC = area under (ROC) curve; HCC = hepatocellular carcinoma; NPV = negative predictive value; PPV = positive predictive value.

We applied our data to other non-invasive models were evaluated for predicting patients with hepatocellular cancer from liver cirrhosis. The 4RLB, MELD, AARP, FI score and FCI had limited diagnostic powers in predicting hepatocellular cancer from liver cirrhosis (AUC = 0.48–0.57), failing to justify further analysis, whilst the Fibro-alpha and PAPAS had useful diagnostic powers in predicting hepatocellular cancer (AUC = 0.70 and 0.80, respectively) but odds ratios were small (data not shown). The most powerful outcomes are shown in Table 4. The HCC-Mark outperformed all other models, showing superior diagnostic performance, the highest AUC (95% CI) and odds ratio (95% CI) for detecting hepatocellular carcinoma.

Discussion

Hepatocellular carcinoma is a systemic disease and required to be evaluated from an integrated viewpoint. Recognizing early-stage hepatocellular cancer is an urgent need to improve patient outcomes and receive more effective therapies [8]. The developed HCC-Mark based on four markers: AFP, hs-CRP, albumin and platelet count for predicting hepatocellular cancer in patients with liver cirrhosis. According to the present study, AFP had 20% sensitivity, a result agreeing with a sensitivity of AFP of 18% to 60% and a specificity of 85% to 90% [5]. Hs-CRP; the second marker is sensitive but non-specific acute phase inflammatory mediator, synthesized by hepatocytes as a response to elevated interleukin 6. Increased CRP is linked with hepatocellular cancer development and progression [24]. In this study, the AUC of hs-CRP was 0.76 for predicting hepatocellular cancer, it was slightly higher than AUCs 0.65 [25] and 0.71 [26] but lower than AUC 0.90 [27] that reported by earlier studies. This variation might be due to the different cut-off value of CRP, ethnic difference, genetic variations or the aetiology of hepatocellular cancer disease (HCV and HBV) [26].

Albumin, the third marker, is produced in the liver, involved in many scoring systems such as

the Child–Pugh, BCLC, CLIP and Okuda scoring systems [28]. Albumin in this study had an AUC 0.66, markedly lower than AUC 0.85 that detected by Attallah et al. [13]. This difference might be related to the difference in population and Child–Pugh score. The platelet count is often reduced in hepatocellular cancer; this could be explained by the destruction by hepatocytes or in the spleen, and is considered an important factor in many non-invasive models [29]. Albumin and CRP has a prognostic value in hepatocellular cancer and is used in several indices such as CRP/albumin and an inflammation-based index IBI [24]. In the present study, HCC-Mark yielded good AUCs in the estimation and validation study, and had a sensitivity and specificity higher than those of AFP alone, confirming its ability to predict early-stage hepatocellular cancer. Staging systems are the primary tool for managing hepatocellular cancer [28]. HCC-Mark can differentiate single focal lesions, absent macrovascular invasion and small-sized hepatocellular cancer <2 from liver cirrhosis. The diagnostic performance of HCC-Mark in the different staging system was analysed to identify the predictive ability for early-stage hepatocellular cancer. HCC-Mark had similar AUCs in BCLC (0-A), CLIP (0–1) and Okuda (stage I) staging systems. Values increased with the hepatocellular cancer progression from early stages to advanced stages of hepatocellular cancer. This data indicated that HCC-Mark is an efficient model in every stage of hepatocellular cancer patients.

Several authors have used fibrotic indices for diagnosing hepatocellular cancer. Abdelgawad et al. [30] compared the accuracies of FIB-4, APRI, age-platelet index (AP), AAR-platelet score (AAR). Moreover, Pang et al. [29] compared the accuracies of FIB-4 and PAPAS in predicting hepatocellular cancer. Mobarak et al. [31] compared the accuracies of eight non-invasive models in predicting hepatocellular cancer; LOK index, AAR, Fibro Q, GUCI, King, APRI, fibro alpha and BRC. In this study, other non-invasive models were evaluated their abilities in predicting hepatocellular cancer, including 4RLB, MELD, AARP, FI, FCI and FRT [4,13,16,32–34], in comparison to HCC-Mark. These validated non-invasive models showed AUC ranged from (0.48–-0.81). HCC-Mark showed superior diagnostic power among other mentioned models with AUC 0.90. Therefore, HCC-Mark is an accurate, non-invasive, simple model and easily calculated with high accessibility. It may be more helpful in the clinical prediction of small size-hepatocellular cancer.

This study represents an advance in biomedical science because the HCC-Mark could be recommended as surveillance modality for the early prediction of hepatocellular cancer.

Summary table

What is known about this topic:

- Early detection of HCC is crucial in order to improve patient outcomes and provide more effective therapies
- The heterogeneous nature of HCC has led to the lack of a single, powerful biomarker for HCC diagnosis
- Many studies have developed a non-invasive diagnostic model for HCC detection

What this work adds:

- HCC-Mark is an accurate and simple non-invasive model for HCC diagnosis from liver cirrhosis
- HCC-Mark is superior to several other scores
- HCC-Mark has good AUCs in early-HCC stages of BCLC, CLIP and Okuda staging system

Disclosure statement

The authors declare no conflict of interest.

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