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Original article

Hepatocellular Carcinoma Multidisciplinary Clinic-Cairo University (HMC-CU) score: A new simple score for diagnosis of HCC

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ABSTRACT

Background and Study Aims: The risk of hepatocarcinogenesis depends on background liver factors, of which fibrosis is a major determinant. Serum markers and scores are of increasing importance in non-invasive diagnosis of hepatic fibrosis. Our aim was to predict the occurrence of hepatocellular carcinoma (HCC) using a non-invasive fibrosis score calculated using routine patient data.

Patients and mthods: Our retrospective study included 1,291 hepatitis C related-HCC Egyptian patients (Group 1) recruited from the multidisciplinary HCC clinic, Faculty of Medicine, Cairo University in the period between February 2009 and June 2016 and 1072 chronic hepatitis C-naïve patients (Group 2) with advanced fibrosis (≥F3) and cirrhosis (F4). King score, Fibro Q score, Aspartate aminotransferase-to-platelet ratio index (APRI), AST to ALT ratio (AAR), LOK score, Göteborg University Cirrhosis Index (GUCI), Fibro-α and Biotechnology Research Center (BRC) scores were calculated for all patients. Regression analysis and receiver operating characteristics (ROC) were used to calculate the sensitivity, specificity and predictive values for significant scores with the best cut-off for predicting HCC. A regression equation was used to calculate predicted probabilities of HCC using the following variables; age, gender, haemoglobin, international normalised ratio (INR), albumin and alpha fetoprotein. The appropriate score cut-off points yielding optimal sensitivity and specificity were determined by ROC curve analysis.

Results: There was a highly significant difference between the two groups for all calculated scores (P = 0.0001). Our new score, the Hepatocellular Carcinoma Multidisciplinary Clinic-Cairo University (HMC-CU) score (Logit probability of HCC = − 2.524 + 0.152*age − 0.121*Hb − 0.696*INR − 1.059*Alb + 0.022*AFP + 0.976*Sex. Male = 1, Female = 0), with a cut-off of 0.559 was superior to other scores for predicting HCC, having a sensitivity of 90% and specificity of 80.6%.

Conclusion: The HMC-CU score is a promising, easily calculated, accurate, cost-effective score for HCC prediction in chronic HCV patients with advanced liver fibrosis.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumour of the liver, with a high incidence and prevalence, especially in Africa [1]. As early detection of HCC provides the best chance for curative treatment, which in turn improves patient survival [2], international guidelines recommend that patients with cirrhosis should undergo periodic surveillance for early detection of HCC [3–7]. Despite its crucial importance, the utilisation of the surveillance programmes is poor, and>60% of HCCs are diagnosed at a late stage, particularly so in low-income countries [8]. This is mostly related to the poor compliance of

Abbreviations: AASLD, American Association for the Study of Liver Diseases; APRI, Aminotransferase-to-platelet ratio index; BRC, Biotechnology Research Center; CI, Confidence interval; CT, Computed tomography; DAA, Direct-acting antiviral; FI, Fibrosis index; INR, International normalized ratio; MRI, Magnetic resonance imaging; ROC, Receiver operating characteristic; SVR, Sustained virological responses, AFP, ALT, AUC, CLIP, GUCI, HCC, HCV, US.

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cirrhotic patients to the surveillance programmes as well as the lack of a sensitive and specific tumour marker [9]. Serum alpha fetoprotein (AFP), the most common marker used for HCC diagnosis, has a low sensitivity for the detection of HCC in at-risk populations [10]. In addition, the AFP test has a high false-positive rate of ~20% among patients with chronic hepatitis, and 20%–50% among those with liver cirrhosis [11].

The American Association for the Study of Liver Diseases (AASLD) Practice Guidelines Committee recommended that ultrasound (US) examination alone (without AFP testing) should be used for HCC surveillance [12]. However, the detection of small HCC lesions in cirrhotic livers by US is much more difficult than the detection of metastases in a normal liver, owing to the disturbed parenchymal architecture [13]. Also, the sensitivity of US in detecting HCC was found to be affected by tumour size. Kim and colleagues concluded that the sensitivity for diagnosing nodules>2 cm in size was 38%, while for lesions < 2 cm it was only 30% [14]. Another study claimed that the sensitivity for detecting tumours with a size smaller than 1 cm was 42% [15]. US has low sensitivity and high specificity in detecting HCC in patients with end-stage liver disease requiring liver transplantation [13]. According to a retrospective study of 200 patients with liver failure who underwent liver transplantation within 90 days of US scanning, correlation of the US findings with the explanted livers revealed a US sensitivity of 75% for large lesions (>5 cm), while it dropped significantly to 13.6%–50% in the detection of smaller lesions (1–5 cm) [16]. For these reasons, we aimed to develop a simple score, using routine patient data, and test its accuracy in the detection of HCC in comparison with the widely used AFP measurements.

Patients and methods

In the current study, we reviewed the data of 2363 Egyptian patients with HCV-related chronic liver disease (CLD); 1,291 patients were diagnosed with HCV-related HCC, while 1072 patients were diagnosed to have HCV-related liver cirrhosis without evidence of HCC lesions.

The diagnosis of HCC was made according to the AASLD practice guidelines [12]. Focal hepatic lesions detected by abdominal ultrasound (US) and/or high s-AFP levels were further evaluated by triphasic multiphase computed tomography or contrast-enhanced dynamic magnetic resonance imaging. Lesions showing evidence of enhancement in the arterial phase and/or delayed wash out were diagnosed as HCC. Diagnosis of HCV-related liver cirrhosis was based on clinical, laboratory, and imaging evidence of chronic liver disease with and without hepatic decompensation or portal hypertension in addition to detection of HCV antibodies and/or HCV RNA.

Aspartate APRI score [17], Fib-4 score [18], LOK score [19], Fibrosis index score [20], King score [21], Fibro Q score [22], AAR (AST to ALT ratio) [23], GUCI (Göteborg University Cirrhosis Index (GUCI)) [24], Fibro-α score [25] and BRC score [26] were calculated for all patients. They were calculated as follows:

- APRI score: (AST/upper limit of normal)/platelet count (expressed as platelets × 109/L) × 100
- LOK score: log odds = −5.56 − 0.0089 × platelet count (103/mm3) + 1.26 × (AST/ALT) + 5.27 × INR
- King score: age (years) × AST (U/L) × (INR)/number of platelets (10^9/L)
- Fibro Q score: [(10 × age (years) × AST × PT-INR)/(PLT × ALT)]
- Aminotransferase/Alanine aminotransferase ratio (AAR): AST (U/L)/ALT(U/L)
- GUCI score: normalised AST × PT-INR × 100/platelet count (10^9/L)
- Fibro-α score: (1.35 (numeric constant) + AFP (IU/mL)) × 0.009584 + AST/ ALT × 0.243 − platelet count (×10^9/L) × 0.001624)
- BRC score: 1.02 + 0.4 × AFP (U/L) + 0.19 × age (years) − 0.02 × platelet count (×10^9/L)

Based on the most relevant factors identified by our regression analysis, a new score was developed: The Hepatocellular Carcinoma Multidisciplinary Clinic-Cairo University (HMC-CU) score. This score was compared with the previously described scores in terms of diagnostic sensitivity and specificity. The HMC-CU score diagnostic accuracy was also compared with s-AFP, since this is a widely used standard diagnostic tool.

Being retrospective in nature, the need for patient consent was waived, as we considered the original consent signed by the patients sufficient, which specifically included their acceptance of the use of their data for future studies. The study was carried out according to the ethical guidelines of the 1975 Helsinki Declaration.

Statistical analysis

Data was analysed using the software SPSS v21.0 for Windows. Categorical variables were summarised by frequency counts and percentages. Continuous variables were represented as means with standard deviations. The comparison between the HCC group (Group 1) and the liver cirrhosis group (Group 2) was done by univariate analysis as follows: Categorical variables were evaluated with the Chi square test; whereas continuous variables were assessed using the independent samples *t*-test. Multivariate analysis was performed to determine factors associated with HCC. Odds ratios were calculated by stepwise logistic regression modelling. Eventually, a regression equation was developed to calculate predicted probabilities of HCC using the following variables; age, gender, haemoglobin, INR, albumin and AFP. A ROC curve was developed to determine appropriate score cut-off points that would give optimal sensitivity and specificity. Hypothesis testing was two-sided, and statistical significance was accepted at the 5% level. Statistical significance was expressed as a probability (P) value.

Results

On bivariate analysis, the HCC patients were significantly older, anaemic, and showed significant thrombocytopenia, hyperbilirubinaemia and elevated s-AST and s-AFP levels. S-albumin was significantly lower in HCC patients. (Table 1). We performed multivariate analysis to determine factors that could be integrated into a formula that could best predict HCC, and which was constructed by logistic regression modelling (Table 2). Hence, the Hepatocellular Carcinoma Multidisciplinary Clinic – Cairo University (HMC-CU) score could be formulated as follows:

Logit probability of HCC = − 2.524 + 0.152*age − 0.121*Hb − 0.696*INR − 1.059*Alb + 0.022*AFP + 0.976*Gender

Gender: Male = 1; Female = 0

The diagnostic value of the HMC-CU score was subsequently assessed by ROC curve analysis. At a cut-off point of 0.56, the HMC-CU score enabled correct identification of patients with HCC with 90% sensitivity and 80.6% specificity. The AUC was 0.93, and the 95% confidence interval (CI) was 0.917–0.94. (Fig. 1). When comparing the diagnostic performance of the HMC-CU score with the performance of s-AFP for early diagnosis of HCC, s-AFP had a sensitivity of 0.698 and a specificity of 0.609 at a cut-off value of 10.05 ng/mL. The AUC was 0.76, and the 95% CI was 0.74–0.78.

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Table 1
Demographic and laboratory features of the study population.

	HCC group (n = 1291)	Liver cirrhosis group (n = 1,072)	*P* value
Age (years)	57.83 ± 5.7	48.2 ± 8.3	**0.001**
Gender			
Male/Female	990/299	609/463	**< 0.001**
Hb (g/dL)	12.2 ± 1.9	12.9 ± 2.3	**0.001**
WBCs (10^3/cmm)	5.9 ± 2.7	5.7 ± 2	0.1
Platelets (10^3/cmm)	132.8 ± 67.1	155 ± 70.2	**0.001**
Bil total (mg/dL)	1.2 (0.3–22)	0.95 (0.2–27.6)	**0.001**
ALT (IU/mL)	49 (3–630)	52 (4–379)	**0.002**
AST (IU/mL)	65 (6–1,155)	58 (4–473)	**0.01**
Alb (g/dL)	3.26 ± 0.6	3.9 ± 0.7	**0.001**
INR	1.28 ± 0.2	1.27 ± 0.4	0.5
AFP (µg/dL)	31.5 (0.5–9,327)	7.7 (0.1–204)	**0.001**

Data are expressed as means ± standard deviations (SD) and medians (range). Hb, haemoglobin; WBCs, white blood cells; Bil total, total bilirubin; ALT, Alanine transaminase; AST, Aspartate transaminase; Alb, albumin, INR, international normalised ratio; AFP, alpha fetoprotein.

Table 2
Multivariate analysis for calculation of the new MHC-CU score.

	OR	95% CI		*P* value
		Lower limit	Upper limit	
Age	1.164	1.141	1.188	<0.001
Gendre	2.653	1.959	3.594	<0.001
Hb	0.886	0.819	0.959	0.003
INR	0.498	0.267	0.931	0.029
AIB	0.347	0.268	0.448	<0.001
AFP	1.022	1.016	1.028	<0.001
Constact	0.080			0.010

OR, Odds Ratio; CI, confidence intervals; Hb, haemoglobin; INR, international normalised ratio; Alb, albumin; AFP, alpha fetoprotein.

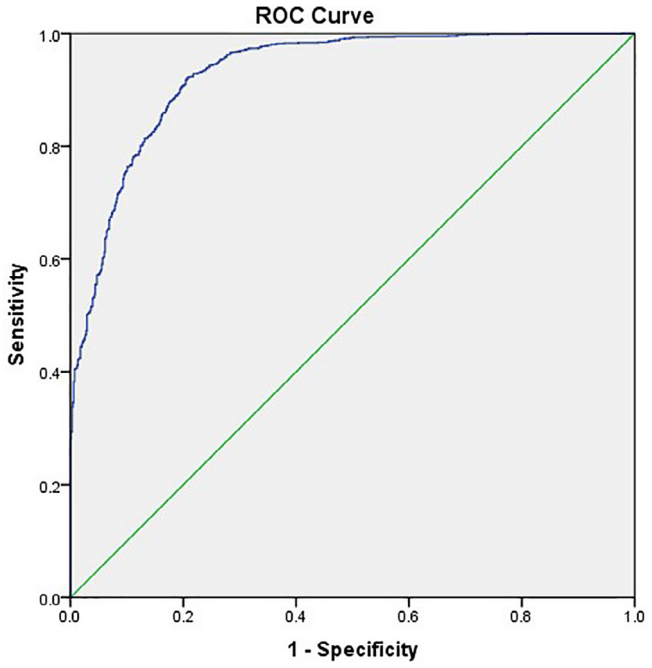

Fig. 1. Receiver operating characteristics (ROC) curve for the Hepatocellular Carcinoma Multidisciplinary Clinic – Cairo University (HMC-CU) score.

Comparisons with the other scores were done, and still, the new HMC-CU score showed the highest sensitivity and specificity for HCC diagnosis (Table 3).

Discussion

HCC is a major health problem that can affect cirrhotic patients and lead to notably reduced quality of life and considerably high mortality rates, which almost reflect HCC incidence rates [27]. In the current era of direct-acting antiviral therapy, sustained virological responses prevent complications of liver cirrhosis such as ascites and encephalopathy; however, several studies confirm the possibility of HCC developing in cirrhotic livers even after HCV eradication. In addition, many patients present with late HCC beyond curative treatment. Early diagnosis of HCC may typically safeguard curative treatment, which would translate into improved survival rates. In the current study, we developed a simple score based on routinely available, simple, non-invasive parameters with a view to accurately predicting the presence of HCC lesions in chronic HCV-infected advanced fibrotic and cirrhotic patients.

S-AFP, a widely used non-invasive marker for HCC [28] was significantly associated with HCC in the bivariate and the multivariate analysis. In a recent study [29], s-AFP was the most decisive variable in the predictive model for HCC. In previously published studies, AFP (with different cut-offs) had a sensitivity of 39%–65%, a specificity of 76%–94%, and a positive predictive value of 9%–50% for diagnosing HCC [30]. The variation in sensitivity and specificity of AFP in the studies performed to date may reflect the diversity of study populations, variations in design, and the use of different cut-off values for normality. The definition of the AFP cut-off level for the diagnosis of HCC has been subject to debate. An AFP value > 400 ng/mL has been considered diagnostic for HCC in cirrhotic patients. However, such a cut-off value is problematic in absolute diagnostic terms, since such high levels are uncommon in patients with small tumours (<5 cm), and only 30% of HCC patients have AFP levels higher than 100 ng/mL. Furthermore, up to 20% of patients with HCC do not produce AFP [31].

In our study, we succeeded in formulating a score for the diagnosis of HCC. This score utilised AFP and other parameters such as age, gender, s-albumin, haemoglobin, and INR levels.

Previous reports identified that age is associated with impaired in DNA repair, which contributes to the development of HCC [32,33]. Age is also related to progression of cirrhotic status, with higher accumulating probabilities of developing HCC over time.

In the present study, male patients were 2.6 times more likely to develop HCC. Omran et al and Degos et al previously reported similar findings [29,34]. Androgens and androgen receptors have been suggested to stimulate and promote HCC [35]. The gender-specific age-adjusted incidence rate ratio ranges from 1.3 to 3.6 worldwide [36].

Albumin is an important factor that has been integrated in several scoring systems, such as the Child–Pugh and CLIP score systems [37]. Hypoalbuminemia increases the risk of HCC development in HBV-related chronic liver disease [38] and significantly increases mortality from HCV-related HCC [39]. As for INR, Al Sawat et al published a study that focused on the characteristics of patients with HCC in Middle Eastern countries and reported that an INR > 2 was a predictor of poor survival in univariate analysis. However, this finding failed to find support by their multivariate analysis [40].

The diagnostic value of the HMC-CU score was assessed by ROC curve analysis. At a cut-off point of 0.56, the HMC-CU score enabled correct identification of patients with HCC with 90% sensitivity and 80.6% specificity. The AUC was 0.93 and the 95% CI was 0.917–0.94. The proposed score depends on s-AFP in addition to routine laboratory parameters. The score is simple, inexpensive, and can easily be used by physicians in their daily practice. Still, validation of our results is needed to further support the applicability of the score.

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Table 3
The sensitivity, specificity, and AUC of the different scores for HCC diagnosis.

Score	Cut-off	Sensitivity	Specificity	AUC	95% CI		*P* value
					Lower limit	Upper limit	
King score	27.24	0.678	0.601	0.676	0.652	0.700	**0.0001**
Fibro Q score	5.01	0.701	0.691	0.743	0.720	0.766	**0.0001**
APRI score	1.15	0.583	0.546	0.591	0.567	0.614	**0.0001**
AAR	1.13	0.590	0.548	0.583	0.560	0.606	**0.0001**
LOK score	0.887	0.675	0.634	0.677	0.655	0.700	**0.0001**
GUCI score	1.38	0.600	0.572	0.613	0.588	0.638	**0.0001**
Fibro-α score	1.58	0.710	0.686	0.788	0.770	0.806	**0.0001**
BRC score	12.34	0.803	0.244	0.871	0.857	0.885	**0.0001**
MHC-CU score	0.559	0.900	0.806	0.929	0.917	0.941	**<0.001**

AUC, area under the curve; HCC, hepatocellular carcinoma; CI, confidence intervals; APRI, Aspartate aminotransferase-to-platelet ratio index; AAR, AST to ALT ratio; GUCI, Göteborg University Cirrhosis Index.

In conclusion, the Hepatocellular Carcinoma Multidisciplinary Clinic – Cairo University (HMC-CU) score may improve the accuracy of HCC screening and surveillance and can be used without extra costs incurred for sophisticated tests.

Conflicts of interests

None declared.

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