RESEARCH ARTICLE

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HCC-miR: A Simple, Noninvasive, and Sensitive Model for Early Diagnosis of HCV-Associated Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and a major cause of cancer-related mortality worldwide. Chronic hepatitis C virus (HCV) infection remains the predominant etiological factor in Egypt. The limited sensitivity and specificity of alpha-fetoprotein (AFP) continue to hinder early HCC detection. This study aimed to assess the diagnostic significance of circulating microRNA-155 (miRNA-155) expression in HCV-related HCC and to develop a novel, noninvasive diagnostic model combining miRNA-155 with routine biomarkers. **Methods:** A total of 42 HCV-positive HCC patients, 83 patients with liver cirrhosis (LC), and 20 healthy controls were enrolled. Clinical, hematologic, and biochemical parameters were analyzed. Circulating miRNA-155 levels were quantified by quantitative real-time PCR and normalized to U6 RNA. Receiver operating characteristic (ROC) curve analysis and multivariate discriminant analyses were used to develop a composite diagnostic model integrating AFP, albumin, platelet count, INR, AST/ALT ratio, and miRNA-155, designated the HCC-miR Score. **Results:** Liver function tests and hematologic indices showed progressive deterioration from controls to LC and HCC groups. miRNA-155 expression was significantly elevated in HCC (6.71 ° 3.38) compared with LC (5.44 ° 2.31) and controls (1.27 ° 0.68) ($p < 0.0001$). The HCC-miR Score demonstrated superior diagnostic accuracy (AUC = 0.753) to AFP alone (AUC = 0.713), achieving 100% sensitivity and 68% specificity at a cutoff value of 0.32. The model effectively discriminated early-stage, small-sized, and well-differentiated tumors from cirrhotic cases, outperforming AFP across all subgroups. **Conclusion:** Circulating miRNA-155 is markedly upregulated in HCV-related HCC and correlates strongly with disease progression. The novel HCC-miR Score represents a simple, sensitive, and noninvasive model for the early diagnosis of HCC in high-risk HCV patients.

Keywords: Hepatocellular carcinoma- Hepatitis C virus- miRNA-155- Alpha-fetoprotein

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Introduction

Hepatocellular carcinoma (HCC) is a major form of liver malignancy and continues to pose a serious global health challenge. It ranks as the fifth most prevalent cancer among men and the seventh among women worldwide, while occupying the second and sixth positions in cancer-related mortality for men and women, respectively [1]. Liver cancer remains the second leading cause of cancer-associated deaths. Only about 30% of patients are candidates for curative interventions such as surgical resection, liver transplantation, or local ablation [2]. Palliative approaches, including transcatheter arterial chemoembolization and sorafenib therapy, are used in advanced stages. Unfortunately, most HCC patients are diagnosed late due to the absence of highly specific and sensitive diagnostic biomarkers for early detection [3, 4]. Consequently, approximately 80% of HCC patients present with advanced disease, and challenges in diagnosis and treatment persist [3]. Although numerous studies have attempted to clarify the molecular mechanisms driving HCC initiation and progression, they remain incompletely understood [5]. Therefore, exploring the molecular pathogenesis of HCC and identifying novel biomarkers and therapeutic targets are essential steps toward improving diagnostic accuracy and treatment outcomes. The discovery of the first microRNA (miRNA) marked a breakthrough in molecular biology. miRNAs are short, single-stranded, non-coding RNA molecules of approximately 18–25 nucleotides [6]. They regulate gene expression post-transcriptionally by binding to the 3′ untranslated regions (3′-UTRs) of target messenger RNAs (mRNAs), resulting in translational inhibition or degradation of the mRNA. miRNAs play crucial roles in multiple biological and pathological processes, including cellular proliferation,

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differentiation, development, and tumorigenesis [7]. Among them, microRNA-155 (miRNA-155) is encoded within the third exon of the *B-cell integration cluster (BIC)* gene located on chromosome 21 [8]. The *BIC* gene itself lacks a protein-coding region, and its overexpression can drive abnormal cell proliferation. Experimental studies have demonstrated elevated miRNA-155 expression across several cancer types where it acts predominantly as an oncogenic factor in tumor development [9]. Recent investigations suggest that miRNA-155 expression correlates with key clinicopathological features of various malignancies and may serve as a biomarker for tumor progression and prognosis [10]. Elevated miRNA-155 expression has been linked to TNM stage, lymph node metastasis, and proliferating cell nuclear antigen (PCNA) positivity in breast cancer [11]. Similarly, it was reported that; high miRNA-155 levels were associated with advanced clinical stages and poor prognosis in pancreatic cancer, where a connection between miRNA-155 and lymph node metastasis in colorectal cancer was reported [12]. Additional studies have demonstrated that miRNA-155 upregulation is related to the development of gastrointestinal malignancies [13]. Nevertheless, the relationship between miRNA-155 expression and the clinicopathological characteristics of HCC has not been fully defined. The present study was aimed to investigate these aspects comprehensively by analyzing miRNA-155 expression in HCC patients and assessing its clinical significance as case-control study. Moreover, a simple noninvasive score based on combination of routine biomarkers and miRNA-155 for early detection of hepatocellular carcinoma progression was developed.

Materials and Methods

Patients

The current study includes 42 patients with liver cirrhosis who have developed hepatocellular carcinoma (HCC). Diagnosis of HCC was based on computed tomography and elevated AFP levels. HCC patients were classified according to the sixth edition of the International Union against Cancer tumor-node-metastasis (TNM) staging system [14]. In addition, 83 chronic hepatitis patients with liver cirrhosis (LC) and bearing no evidence of malignancy, which is confirmed by golden standard tests. All patients were recruited from Capital University Hospital, Badr City, Cairo, and Damietta Cancer Institute, Damietta, Egypt from November 2017 till April 2019. Patients were subjected to full clinical examinations, radiologic investigations (including abdominal ultrasonography and triphasic computed tomography) and laboratory investigations. Inclusion criteria of all studied cases (HCC and LC) were HCV-positive as confirmed by polymerase chain reaction (PCR) and serologic tests. Moreover, all participants were sero-negative for hepatitis B surface markers (HBsAg, HBeAg, and HBcAb) and HBV antibodies. In addition to 20 healthy individual for compression purposes. Exclusion criteria including HCV/HBV coinfection as well as evidence of other malignancies. Written informed consent was obtained from all participants prior to enrollment in the study, which conformed to the ethical guidelines of the 2004 Declaration of Helsinki.

Blood Samples

Peripheral blood samples (5 mL) were collected from patient and control subjects in Cell-Save blood collection tubes (Immunicon Inc., Huntingdon Valley, PA, United States) containing EDTA and a cellular preservative. From each subject, one tube was used for assessment of hematological and biochemical parameters and the other was used for RNA and DNA extraction. Platelet count was performed on a D-cell 60 Automated Hematology Analyzer (Diagon Ltd, Budapest, Hungary). Liver function tests (albumin, total bilirubin, AST and ALT) were all measured on an automated Biochemistry Analyzer (A15; Biosystem, Barcelona, Spain). AFP level was determined by chemiluminescence using the Immulite AFP (1000) kit (Mini-Vidas, France).

Detection of HCV and HBV

Total viral DNA/RNA isolation was performed using QIAamp MinElute Virus Spin Kit (Qiagen, Venlo, Limburg, Germany). HBV-DNA was analyzed by PCR as previously described [15]. HCV-RNA detection and quantification were done using a StepOne Real-Time PCR system (Applied Biosystems of Thermo Fisher Scientific Inc., Waltham, MA, United States) following the manufacturer's instructions.

Detection of miRNA-155

Blood samples from each group were utilized to investigate the expression levels of circulating miRNA-155. The TRIzol reagent (Invitrogen, USA) was applied to extract total RNA from serum [16]. Using SYBR Green master mix (Qiagen/SABiosciences Corporation, USA), 1 µg of RNA samples were reverse transcribed into complementary DNA (cDNA) using the RT kit (Applied Biosystems, Foster City, CA, USA). Quantitative real-time PCR (qRT-PCR) was performed using StepOne RT-PCR (Thermo Scientific, USA) under standard cycling conditions. Each reaction was carried out in triplicate, with U6 acting as an endogenous control for miRNA normalization [17]. Primers sequences for miRNA-155 was F: 5′-GCGGTTAATGCTAATCGTGATA-3′, R: 5′-CGAGGAAGAAGACGGAAGAAT-3′ [18] and for U6 was F: 5′-GCTTCGGCAGCACATATACTAAAAT-3′, R: 5′-CGCTTCACGAATTTGCGTGTCAT-3′ [19]. The $2^{-\Delta\Delta Ct}$ method was employed to assess relative gene expression. The purity and concentration of RNA were evaluated using a Nanodrop spectrophotometer, and only samples with an A260/A280 ratio between 1.8 and 2.0 were included.

Statistical analysis

Statistical analysis was performed using MedCalc version 11.3.3.0 (MedCalc Software Ltd, Ostend, Belgium). Data were expressed as mean ° standard deviation (X ° SD), and significance was considered at $p < 0.05$. Mann–Whitney U test was used for comparisons between independent groups. Receiver operating characteristic (ROC) curves were plotted to assess and

compare the diagnostic accuracy of biochemical markers for discriminating HCC from chronic hepatitis. The multivariate discriminant analysis (MDA) was carried out stepwise using the minimum Wilks' lambda method. Sensitivity, specificity, and accuracy were calculated accordingly.

Results

Patient's characteristics

The clinico-pathological data (Table 1) demonstrate a clear biochemical and hematological deterioration from healthy controls to cirrhotic and HCC patients. Significant elevations in AST, ALT, bilirubin, INR, AFP, and APRI values were observed in HCC compared with both liver cirrhosis and healthy groups ($p < 0.0001$), reflecting progressive hepatic injury, impaired synthetic function, and tumor-associated metabolic activity. Conversely, albumin and platelet counts showed marked declines in HCC patients, indicating advanced hepatic dysfunction and portal hypertension. The higher mean age in the HCC group (50.4 ° 10.7 years) compared with cirrhotic and control subjects also aligns with the age-dependent accumulation of carcinogenic risk.

Importantly, miRNA-155 expression increased progressively from controls (1.27 ° 0.68) to cirrhotic (5.44 ° 2.31) and reached its highest level in HCC tissues (6.71 ° 3.38), with a highly significant difference ($p < 0.0001$). This upregulation supports its proposed oncogenic role and indicates a potential contribution to hepatic carcinogenesis and disease progression. The tumor characteristics of the HCC group predominantly large size (> 5 cm in 76%), advanced stage (III + IV in 29%), and presence of vascular invasion (29%) suggest a cohort with substantial tumor burden, providing a suitable context for evaluating circulating or tissue biomarkers.

Diagnostic performance using area under the ROC curves

ROC curve analysis was performed to assess and compare the diagnostic utility of multiple biomarkers

Table 1. Clinico-Pathological Data of Healthy Individuals and Patients with Chronic Hepatitis and Hepatocellular Carcinoma

Variable	Healthy control (n= 20)	LC patients (n= 83)	\HCC patients (n = 42)	*P value
Age (years)	41.3 ± 6.2	39.1 ± 8.7	50.4 ± 10.7	< 0.0001
AST (U/L)	14.4 ± 9.6	43.2 ± 11.4	91 ± 12.8	< 0.0001
ALT (U/L)	16.7 ± 10.1	51.4 ± 13.1	105 ± 11.4	< 0.0001
AST/ALT (AAR)	0.33 ±0.06	0.82 ± 0.06	0.91 ± 0.09	0.005
Albumin (g/dl)	4.8 ± 0.41	4.2 ± 0.63	2.7 ± 0.57	< 0.0001
Total Bilirubin (mg/dl)	0.82 ±0.34	1.01 ± 0.31	3.1 ± 0.31	< 0.0001
Platelets count ($\times 10^9$)/L	311 ± 66	141 ± 57	48 ± 14	< 0.0001
INR	0.78 ± 0.21	1.7 ± 0.34	2.6 ± 0.55	< 0.0001
AFP (U/L)	1.2 ± 3.02	8.5 ± 2.1	231 ± 23	< 0.0001
APRI	0.31 ± 0.08	2.1 ± 0.31	2.8 ± 0.71	< 0.0001
miRNA-155	1.27 ± 0.68	5.44 ± 2.31	6.71 ± 3.38	< 0.0001
Tumor stage, n (%)				
I + II			30 (71)	
III + IV			12 (29)	
Tumor encapsulation, n (%)				
Non			27 (64)	
Complete			15 (36)	
Tumor grade,n (%)				
I			22 (52)	
II + III			20 (46)	
Tumor size, n (%)				
< 5cm			10 (24)	
>5 cm			32 (76)	
Vascular invasion, n (%)				
Absent			30 (71)	
Present			12 (29)	
Number of Lesion, n (%)				
Single			27 (64)	
Multiple			15 (36)	

*P> 0.05 considered not significant (NS), P< 0.05 considered significant. The reference group of p value were hepatocellular carcinoma (HCC) group and liver cirrhosis (LC) group. INR: international normalized ratio, AFP, alpha fetoprotein; APRI, [AST(U/L)/(40)]/[Platelet count $\times 10^9$/L]×100; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Variables were expressed as mean ± SD.

in order to find the best biomarkers to be chosen in our combination score. Parameters include INR, Albumin, AST/ALT, Platelet count, AFP, and miRNA-155. The most effective biomarkers with high area under curves were as follows in descending order: AFP (0.731) > Platelet count (0.710), INR (0.664), Albumin (0.639) > miRNA-155 (0.611)> AST/ALT Ratio (0.601), Figure 1.

Multivariate analysis and predictive model

A predictive model was constructed using multivariate discriminant analysis. In order to enhance the diagnostic performance of AFP to be able to differentiate HCC patients from those with LC, we combined AFP with the other biomarkers of high AUC (mentioned previously). Simply, we started combination by combining two biomarkers (AFP and miRNA-155), then combining three biomarkers (AFP, miRNA-155 and ALT), then four biomarkers (AFP, miRNA-155, ALT, and Albumin) then five biomarkers (AFP, miRNA-155, ALT, and Albumin, and Platelet count), finally six biomarkers AFP, miRNA-155, ALT, and Albumin, Platelet count and INR). Multivariate discriminate analysis selects the most potent model for early prediction of HCC among hepatitis C virus patients. Our proposed model is named HCC-miRNA-155 Score. HCC-miR Score = AFP (U/L) - Albumin (g/dl) × 0.07 - Platelet count ($\times 10^9$)/L × 0.003 + miRNA × 0.01 + INR × 0.003. – AST/ALT Ratio × 0.2. The score had a wide range from 0.02 to 1.19 and it showed high significance ($P < 0.001$, Figure 2) to differentiate patients with HCC from liver cirrhosis patients HCC-miR Score was calculated for each individual, it produced the highest AUC to differentiate HCC patient from those with liver cirrhosis (0.753) compared to AFP (0.713). The highest sensitivity (100%) and specificity (68%) was taken at a cut-off 0.32, where above 0.32, patient is considered with HCC and below 0.32, patient is considered with liver cirrhosis. Further, sensitivity of AFP for detection of HCC after implantation to the new developed score was shifted from 55% to 94% (Figure 3).

Table 2. Diagnostic Performance of HCC-miR-155 Score against Tumor Burden in Hepatocellular Carcinoma

Clinical data	HCC- miR Score			
	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC
Tumor stage				
I + II	89	81	76	0.748
III + IV	71	76	69	
Tumor encapsulation				
Non	82	75	65	
Complete	70	71	81	0.711
Tumor grade				
I	69	69	83	0.892
II + III	75	81	79	
Tumor size				
< 5cm	87	87	84	0.789
> 5 cm	81	68	75	
Vascular invasion				
Absent	71	85	82	0.879
Present	85	86	75	
Number of Lesion				
Single	84	71	69	0.789
Multiple	75	65	81	

Diagnostic performance HCC-miR Score in comparison with AFP

The diagnostic utility of HCC-miR Score and AFP against tumor burden were illustrated in Table 2 and Table 3. The diagnostic power of HCC-miR Score was the better one for discriminating patients with HCC from

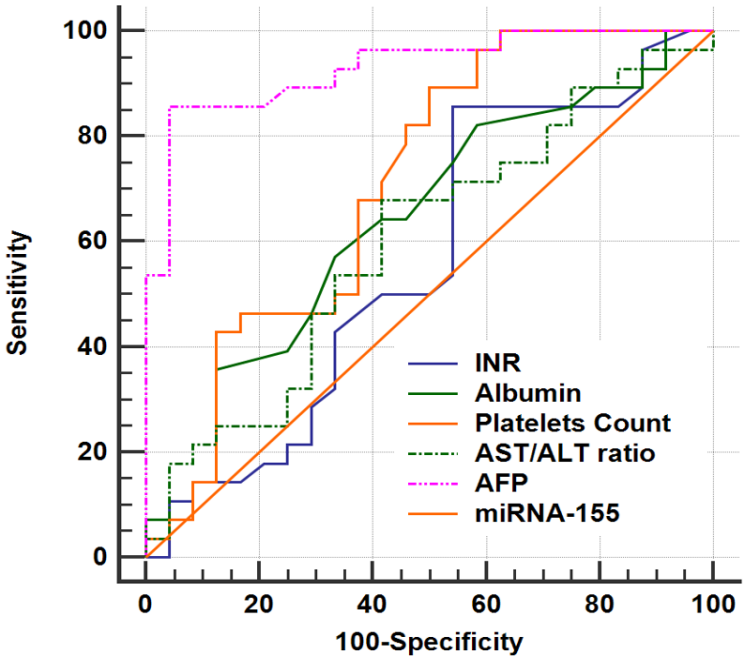

Figure 1. ROC Curve Analysis for Candidate's Biomarkers Including INR, Albumin, Platelets count, AST/ALT Ratio, AFP and miRNA-155 for differentiation between patients with hepatocellular carcinoma and liver cirrhotic patients.

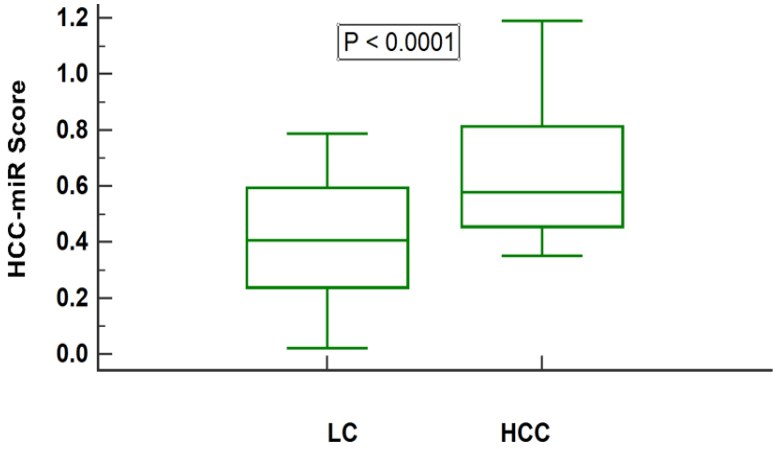

Figure 2. Box Plots of HCC-miR Score to Discriminate HCC Patients from Those with Liver Cirrhosis. The box represents the interquartile rang. The Whiskers indicate the highest and lowest values, and the line across the box indicates the median value.

Table 3. Diagnostic Performance of AFP Score against Tumor Burden in Hepatocellular Carcinoma

Clinical data	AFP			
	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC
Tumor stage				
I + II	61	81	69	0.544
III + IV	72	79	73	
Tumor encapsulation				
Non	74	67	68	
Complete	81	71	84	0.587
Tumor grade				
I	78	74	73	0.685
II + III	83	69	79	
Tumor size				
< 5cm	79	73	81	0.511
> 5 cm	85	71	75	
Vascular invasion				
Absent	74	87	75	0.587
Present	76	89	68	
Number of Lesion				
Single	88	61	77	0.611
Multiple	79	83	81	

those with liver cirrhosis compared to AFP alone (AUC were 0.753 and 0.713, respectively). The AUCs of HCC-miR Score for differentiating patients with low TNM stage, complete capsulation, low grade, small tumor size, absence of vascular invasion and single focal lesions from patients with non-malignancy (0.784, 0.711, 0.892, 0.789, 0.879 and 0.789, respectively) which were better than AFP (0.544, 0.587, 0.685, 0.511, 0.578 and 0.611, respectively).

Discussion

Chronic hepatitis C virus (HCV) infection plays a crucial role in the development of both liver cirrhosis and hepatocellular carcinoma (HCC). The serum marker

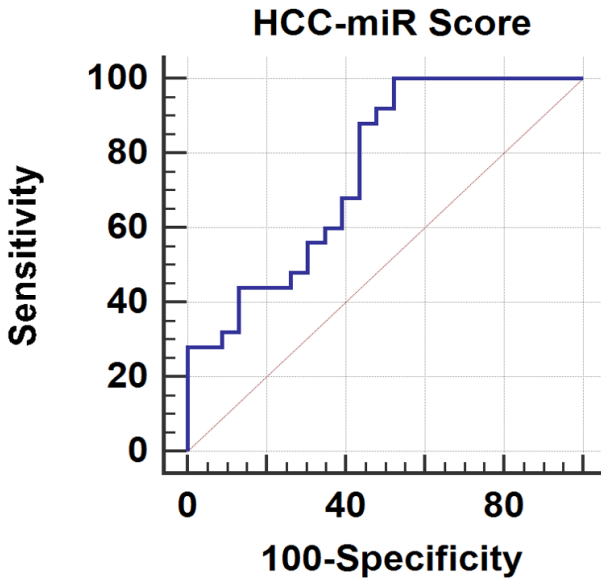

Figure 3. ROC Curve Analysis HCC-miR Score with AUC (0.753), Sensitivity (100%), Specificity (68%) and cut-off (0.32).

alpha-fetoprotein (AFP) remains a recommended tool for HCC surveillance, either alone or in combination with imaging techniques. However, due to its limited sensitivity for accurate HCC diagnosis, numerous efforts have been made to enhance its diagnostic performance, particularly for early detection among high-risk hepatitis patients. In the present study, all HCC patients were positive for HCV infection and had already developed cirrhotic changes in liver tissue. Several diagnostic indices have been proposed to improve HCC detection; however, most rely on conventional biomarkers that primarily reflect hepatic dysfunction rather than tumor-specific processes. These indices are therefore suboptimal, as many parameters within them are influenced by other pathological conditions. For this reason, our study focused on identifying biomarkers that more directly reflect tumor progression. The selected biomarkers were chosen for their simplicity, noninvasiveness, and higher diagnostic accuracy for HCC arising in the background

of chronic HCV infection [20]. An ideal HCC biomarker should demonstrate both high specificity and sensitivity for malignant transformation, while being minimally expressed in nonmalignant cirrhotic states. One of the central focuses in recent hepatocellular carcinoma (HCC) research has been to clarify the relationship between miRNA-155 expression and tumor progression. In this study, miRNA-155 expression was found to be upregulated in HCC tissues, in agreement with the findings reported by Hu et al [21]. The current study aimed to develop an innovative, noninvasive diagnostic model designated the HCC-miRNA-155 Score for the early detection of HCC among patients with chronic HCV infection. To maximize its clinical utility, routine biomarkers were incorporated into the model. Moreover, the analysis revealed significant correlations between elevated miRNA-155 expression HCC patients, consistent with the observations of Song et al [22] in breast cancer. Mechanistically, these findings support the hypothesis that miRNA-155 contributes to tumor progression by downregulating multiple tumor-suppressor genes, including the SRY-related high mobility group box genes [23, 24] and suppressor of cytokine signaling 1 [25] , thereby promoting proliferation and invasion in hepatic cancer cells.

Surgical resection remains the primary treatment option for HCC [26]. However, recurrence rates within the first postoperative year are notably high and often associated with poor prognosis, thus defining recurrence within one year as early recurrence [27]. There is growing evidence linking miRNA-155 expression to HCC prognosis [28]. Huang et al [29] reported that elevated miRNA-155 expression correlated with poorer five-year RFS following radical surgery, with patients exhibiting high miRNA-155 levels showing significantly shorter survival (hazard ratio = 2.002; 95% CI, 1.324–3.027). The findings suggest that miRNA-155 could serve as a promising biomarker for disease characterization and a potential therapeutic target in hepatocellular carcinoma. Our score also included several routine biomarkers. Platelet count was also considered, as thrombocytopenia is common in HCC patients, often due to decreased thrombopoietin synthesis, splenic sequestration secondary to portal hypertension, or the myelosuppressive effect of chronic HCV infection [30]. In our study, platelet counts were significantly lower in HCC patients compared with cirrhotic subjects. Furthermore, Platelet can be activated by tumor-derived factors, contributing to tumor growth through the release of granule contents [31]. Platelet granules also aid in immune evasion by shielding tumor cells from natural killer (NK) cell recognition and by transferring MHC class I antigens to the tumor surface [32]. Therefore, platelet count was integrated into our score to reflect both liver function and malignant transformation. Serum albumin, a key hepatic synthetic product, serves as an important indicator of liver functional reserve. Decreased albumin levels indicate hepatic impairment and are routinely used in clinical scoring systems such as Child–Pugh and CLIP [33]. In our study, serum albumin was markedly reduced in HCC patients compared to those with cirrhosis, thus warranting inclusion as a diagnostic variable in the score. In summary, this study provides the first clinical validation of a diagnostic model combining five biomarkers miRNA-155, ALT, Platelet count, Albumin and AFP to enhance the accuracy of HCC detection among high-risk HCV patients. The proposed HCC-miR Score represents a promising, noninvasive blood-based tool for early HCC diagnosis, particularly in AFP-negative cases. The ability of this score to discriminate HCC from cirrhosis and from healthy individuals may significantly improve early detection and reduce reliance on invasive liver biopsy. Further validation in larger, multicenter cohorts is warranted to confirm its clinical applicability and diagnostic power.

Author Contribution Statement

MA and HS considered equal contribution as first author, perform experimental methods, ME supply us with clinical samples, AE, perform statistical analysis MA and HE prepare the manuscript. All authors review and approve the manuscript.

Acknowledgements

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

All procedures performed in in the study followed the relevant ethical standards of the institutional national research committee (Ethics Board of Capital University) The serial registration number for this study is REC-Sci-HU/C230-051403.

Conflicts of Interests

The authors declare that they have no conflicts of interests.

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