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ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Dr. Ji is a Distinguished Professor in Shanghai University of Traditional Chinese medicine, Shanghai, China. Having received his Bachelor degree from Yangzhou College of medicine in 1991, Dr. Ji undertook his postgraduate training first at Hubei College of Traditional Chinese medicine, received his Master degree in 1994, and then at Shanghai University of Traditional Chinese medicine, received his PhD in 1997. He became Chief Physician in the Gastroenterology Division, Longhua Hospital affiliated to Shanghai University of Traditional Chinese medicine since 2004. His ongoing research interests are applying Evidence-based medicine methods to study the effects, and managing the disease-syndrome pattern establishment of integrative medicine on digestive diseases. Currently, he is the President of the Shanghai Association for the Study of the Liver with integrative medicine.

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Non-invasive tests for the prediction of primary hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world and it is one of the main complications of cirrhosis and portal hypertension. Even in the presence of a well-established follow-up protocol for cirrhotic patients, to date poor data are available on predictive markers for primary HCC occurrence in the setting of compensated advanced chronic liver disease patients (cACLD). The gold standard method to evaluate the prognosis of patients with cACLD, beyond liver fibrosis assessed with histology, is the measurement of the hepatic venous pressure gradient (HVPG). An HVPG ≥ 10 mmHg has been related to an increased risk of HCC in cACLD patients. However, these methods are burdened by additional costs and risks for patients and are mostly available only in referral centers. In the last decade increasing research has focused on the evaluation of several, simple, non-invasive tests (NITs) as predictors of HCC development. We reviewed the currently available literature on biochemical and ultrasound-based scores developed for the non-invasive evaluation of liver fibrosis and portal hypertension in predicting primary HCC. We found that the most reliable methods to assess HCC risk were the liver stiffness measurement, the aspartate aminotransferase to platelet ratio index score and the fibrosis-4 index. Other promising NITs need further investigations and validation for different liver disease aetiologies.

Key words: Non-invasive test; Fibrosis-4 index; Hepatocellular carcinoma; Liver stiffness measurement; Spleen stiffness measurement; Albi

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Core tip: Poor data are available for the prediction of hepatocellular carcinoma in patients with compensated advanced chronic liver disease. Nowadays there is an increasing need for non-invasive tests for stratifying the risk of hepatocellular carcinoma. The most reliable tests for this purpose are the liver stiffness measurement, the aspartate aminotransferase to platelet ratio index score and the fibrosis-4 index, which more accurately assess liver fibrosis. Further research is needed to validate these encouraging results and to address the role of additional non-invasive tests to better evaluate portal hypertension degree in different liver disease aetiologies.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, representing about 90% of the cases^[1]. It is the fifth most common malignant tumor in the world and the third most frequent cause of cancer-related death globally, with more than 600000 deaths per year^[2-5]. Liver cirrhosis represents a major risk factor for HCC; indeed, 90% of hepatocellular carcinomas are related to cirrhosis and one-third of cirrhotic patients develop HCC during their lifetime^[2,5].

The major driver of the HCC development is the degree of liver fibrosis, historically assessed with a semi-quantitative histologic evaluation^[6,7], even though sampling variability and underrepresentation of liver biopsy^[8] hampers its robust determination^[9]. Exceptions to this postulate are mainly represented by HCC arisen in hepatitis B^[10] and non-alcoholic fatty liver disease^[11], since their carcinogenetic mechanisms are less dependent on liver fibrosis. Nowadays liver biopsy, previously considered the diagnostic method of choice for evaluating liver fibrosis, is a procedure confined only to specific and limited diagnostic questions in complex liver diseases^[12]. Indeed, several limitations for its extensive use have been reported, besides the need for physician and pathologists with high expertise, it is a costly and invasive procedure^[12].

Moreover, HCC develops more frequently in patients with cirrhosis complicated by portal hypertension (PH), since PH plays an important role in liver carcinogenesis. Currently, the measurement of the hepatic venous pressure gradient (HVPG) represents the gold standard method for predicting the progression of cirrhosis and the occurrence of its complications, including HCC^[13,14]. Only two studies explored the predictive role of HVPG for primary HCC development; in the first by Ripoll *et al*^[14] the authors concluded that an HVPG ≥ 10 mmHg was able to predict primary HCC development; in parallel, Kim *et al*^[15] in a cohort of alcoholic liver disease patients also concluded that HVPG can be used to predict the development of HCC. However, HVPG is an invasive and risky method and it is not available in all liver units. For these reasons, several research groups have proposed to use non-invasive tools (NITs) as an alternative to liver biopsy and HVPG for predicting the development of primary HCC. The increasing need for NITs in several scenarios of patients with liver cirrhosis has also been recently addressed by the guidelines of the European Society for the Study of the Liver^[12]. The aim of this review is to summarize the available literature on the recent advances in the evaluation of the different non-invasive tests for predicting primary HCC occurrence.

BIOCHEMICAL-BASED NITs

Aspartate aminotransferase to platelet ratio index

The aspartate aminotransferase (AST) to platelet ratio index (APRI) is a biochemical score which has a potential utility in predicting the risk of primary HCC^[16]. The APRI

was introduced by a study by Wai *et al*^[17] and can be calculated using the following formula: $\text{AST (UI/L)} \times [100/\text{platelet count (} 10^3/\text{mm}^3\text{)}]$. In a meta-analysis on hepatitis C virus (HCV)-patients pooling data on APRI, an APRI value > 1.5 had the greatest predictive value for diagnosing cirrhosis, whereas a value < 0.5 for ruling-out the presence of cirrhosis^[18]. Thus, this score was developed as a non-invasive predictor of the progression to fibrosis in patients with chronic viral hepatitis. Over the years, several studies validated its role as markers of hepatic fibrosis^[19,20] and subsequently tested its ability in predicting HCC (Table 1)^[16,20-39].

One of the first correlation between APRI and HCC development was assessed by Hann *et al*^[34] among hepatitis B virus (HBV) patients; APRI was shown to be a good prospective predictor of HCC, especially in the multivariate analysis (P trend = 0.008 in quartile analysis). In a later study by Kim *et al*^[36] including 542 HBV patients, the authors reported an area under the receiver operative characteristic (AUROC) of 0.731 for APRI in predicting HCC, using a cut-off of 0.766.

In a study by Chen *et al*^[35] the authors reported at multivariate analysis a prognostic role for APRI in both patients achieving or not sustained virologic response (SVR) in patients treated with peginterferon/ribavirin: In particular a post-treatment APRI ≥ 0.5 was associated with a hazard ratio (HR) of HCC development of 4.401 in SVR patients, whereas an APRI ≥ 1.5 with an HR of 10.905 in not SVR patients. Similarly, Ji *et al*^[24] analyzed HCV patients who had achieved SVR after interferon-based antiviral treatment, showing that a post-treatment APRI ≥ 1.5 was associated with a higher incidence of HCC ($P < 0.01$). On the other hand, as new direct antiviral agents (DAA) are available, APRI index is lowered after the achievement of SVR^[40], but still holds its predictive value in for HCC occurrence, even after SVR^[29].

The prognostic value of APRI has been reported also in other settings beyond viral hepatitis. Kim *et al*^[26] reported in a cohort of patients with alcoholic liver cirrhosis an AUROC of 0.61 for predicting HCC occurrence at 3 years. Cheung *et al*^[22] also investigated the link between APRI and HCC development in patients with primary biliary cholangitis treated with ursodeoxycholic acid: An APRI at 1 year after treatment (APRI-r1) > 0.54 resulted as an independent risk factor for HCC (HR = 3.94, $P = 0.043$) with an AUROC of 0.77. In conclusion, since APRI cut-offs for cirrhosis suffers of poor sensitivity it is very likely that also the predictive role for HCC development could be underestimated^[41]. Several authors recommended APRI should be considered when liver stiffness measurement (LSM) is unavailable. On the other hand, in such conditions when a transaminase flare could be expected, the use of APRI is rather recommended^[42]. However, we advise the use of this simple transaminase-based NIT which allows us to detect significant fibrosis and to stratify the risk of HCC only in resource-limited settings.

Fibrosis-4 index

The fibrosis-4 index (Fib-4) index was firstly proposed by Sterling *et al*^[43] in a human immunodeficiency virus (HIV)/HCV cohort to assess the degree of hepatic fibrosis and it is based on four factors, included in the following equation: $[\text{age (years)} \times \text{AST (UI/L)}]/[\text{platelet count} \times \text{ALT (UI/L)}]$. A Fib-4 > 3.25 had a high specificity for ruling-in cirrhosis, while a value < 1.45 was the cut-off to rule-out cirrhosis.

As far as Fib-4 is concerned, various authors^[44-48] have assessed its predictive value for primary HCC development (Table 2)^[16,20,23,25-27,32,36,44-60].

Tseng *et al*^[48] evaluated if Fib-4 was able to rule-out HBV patients at lower risk of HCC development; considering treatment-naïve patients, those with a baseline Fib-4 < 1.29 had a significantly lower HCC risk, compared to those with baseline Fib-4 values ≥ 1.29 (HR 5.56, 95%CI: 3.93-7.86). Among patients who received nucleoside analogues (NUC) treatments, none of 326 subjects with baseline Fib-4 < 1.29 , ALT < 40 U/L, and HBsAg < 1000 IU/mL developed hepatocellular carcinoma. Therefore, a cut-off value of Fib-4 < 1.29 showed a good prognostic performance.

Interesting results were also reported in two different studies by Suh *et al*^[46,47]. The first one was conducted on chronic hepatitis B carriers^[46]: It was observed that, compared to subjects with Fib-4 < 1.25 , subjects with Fib-4 between 1.7 and 2.4 had an adjusted HR of 4.57 (95%CI: 1.50-13.92), and subjects with Fib-4 ≥ 2.4 had an aHR of 21.34 (95%CI: 7.73-58.92) for HCC occurrence. In addition, Fib-4 was shown to have incremental predictive value to US-liver cirrhosis for HCC development (C-index: 0.701 vs 0.831, $P = 0.001$). Fib-4 resulted also a better predictor of HCC incidence, compared to US-liver cirrhosis (C-index: 0.775 vs 0.701, $P = 0.040$).

Kanwal *et al*^[45] evaluated a cohort of subjects with HCV-related disease, previously treated with DAAs reaching SVR; the group with Fib-4 > 3.25 showed an annual HCC incidence of 2.16%, against 0.45% among those with Fib-4 ranging from 1.45 to 3.25, and 0.3% of those with Fib-4 ≤ 1.45 . Similar results came from a very large study from North America^[56] exploring Fib-4 variations after SVR: a decrease in Fib-4 scores from ≥ 3.25 pre-SVR to < 3.25 post-SVR halved the risk of HCC. Interestingly, in this

Table 1 Studies reporting the role of aspartate aminotransferase to platelet ratio index in predicting hepatocellular carcinoma

Ref.	Etiology	Patients(n)	Follow-up (mo)	Region	HCC(n)	AUROC	Cut-off
Yu et al ^[31] , 2006	HCV IFN-based treated	776	62.5	Asia	41	0.870	0.75 all patients 0.5 SVR, 1.5 no-SVR
Yu et al ^[31] , 2006	HCV untreated	562	61.8	Asia	54	0.715	1.5
Reddy et al ^[33] , 2015	HCV SVR IFN-treated	22	96	America	0	-	-
Reddy et al ^[33] , 2015	HCV untreated	203	96	America	51	-	-
Hann et al ^[34] , 2015	HBV	855	52.4	America; Asia	82	-	-
Chen et al ^[35] , 2016	HCV SVR	540	41.4	Asia	15	-	> 0.5
Chen et al ^[35] , 2016	HCV (no-SVR)	183	36.8	Asia	14	-	> 1.5
Kim et al ^[36] , 2016	HBV	542	60	Asia	68	0.731	> 0.766
Lee et al ^[37] , 2016	HCV	598	61.2	Asia	8	-	1
Ng et al ^[38] , 2016	HCV	105	40.56	Asia	15	-	2
Wu et al ^[39] , 2016	HCV SVR	1351	6 after SVR	Asia	49	-	0.7
Toyoda et al ^[21] , 2017	HCV SVR; Training cohort	522	104	Asia	21	-	0.73
Toyoda et al ^[21] , 2017	HCV SVR; Validation cohort	309	87,6	Asia	17	-	0,73
Cheung et al ^[22] , 2017	PBC	144	82.8	Asia	12	0.77	0.54
Nishikawa et al ^[23] , 2017	HBV	338	59.8	Asia	33	0.601	0.78
Ji et al ^[24] , 2017	HCV SVR	34	41.4	Asia	5	-	1.5
Paik et al ^[16] , 2018	HBV	1006	61.2	Asia	36	0.76	0.5
Chang et al ^[25] , 2018	HCV (no-SVR)	800	53.5	Asia	100	-	2.57
Kim et al ^[26] , 2018	ALD	924	36	Asia	83	0.61	1
Song et al ^[27] , 2018	HBV	1014	46.8	Asia	37	-	0.5
Sou et al ^[28] , 2018	HCV SVR; IFN-treatment	1351	6 after SVR	Asia	47	-	0,7
Sou et al ^[28] , 2018	HCV no SVR	536	6 post treatment	Asia	75	-	0,7
Na et al ^[20] , 2019	HCV SVR	295	89.2	Asia	12	0.89	2
Yoshimasu et al ^[29] , 2019	HCV DAAs	211	6 after DAAs	Asia	2	-	-
Sahin et al ^[30] , 2019	HBV; HBV+HDV	361	-	Europe	115	-	-
Kim et al ^[32] , 2020	HBV	444	94.2	Asia	25	0.572	-

HCC: Hepatocellular carcinoma; AUROC: Area under receiving operating characteristics curve; HCV: Hepatitis virus C; IFN: Interferon; SVR: Sustained virologic response; HBV: Hepatitis virus B; PBC: Primary biliary cholangitis; ALD: Alcoholic liver disease; DAA: Direct acting antiviral agents; HDV: Hepatitis D virus.

study^[56] even in patients without cirrhosis and with a low risk of HCC, a pre-SVR Fib-4 score ≥ 3.25 (HCC risk 1.22%/year) and post-SVR Fib-4 scores ≥ 3.25 (HCC risk 2.39%/year) were associated with a high risk of HCC up to 10 years after SVR.

The same cut-off values used by Kanwal et al^[45] were applied in a study by Park et al^[44] which studied patients with HIV infection, most of whom had also HBV/HCV infection or history of alcohol abuse; in this cohort, the elevation of Fib-4 proved to be a strong predictive factor for HCC development (HR 3.6 for Fib-4 1.45- 3.25; HR 9.6 for Fib-4 > 3.25; $P < 0.0001$).

The second study of the aforementioned by Suh et al^[47] was conducted on alcohol drinkers: compared to patients with Fib-4 values < 1.00, patients with Fib-4 values ≥ 1.75 and < 2.10 and patients with Fib-4 values ≥ 2.10 showed an aHRs of 5.18 (95%CI: 1.12-24) and 13.63 (95%CI: 3.77-49.33), respectively, for HCC development. Similarly, Fib-4 was a better predictive tool for HCC development if compared to US-assessed liver cirrhosis (C-index, 0.665 vs 0.527, $P = 0.044$).

As non-alcoholic fatty liver disease (NAFLD) is concerned, a study^[57] from four European primary care databases representing the UK, the Netherlands, Italy and Spain, including 18 million adults, found that patients with NAFLD and non-alcoholic steatohepatitis (NASH) with high Fib-4 (>2.67) score had an increased risk for HCC development compared to those with low Fib-4 (HR 25.2).

From a critical point of view, similarly to other serologic markers used in the evaluation of liver fibrosis, Fib-4 has some limitations, mainly because the index is influenced by age, race and could underestimate the presence of fibrosis in

Table 2 Studies reporting the role of fibrosis-4 index in predicting hepatocellular carcinoma

Ref.	Etiology	Patients (n)	Follow-up (mo)	Region	HCC (n)	AUROC	Cut-offs
Park <i>et al</i> ^[44] , 2011	HIV with HCV, HBV, ALD	22980	-	United States	112	-	1.45-3.25; > 3.25
Chon <i>et al</i> ^[49] , 2012	HBV	1126	30.7	Asia	63	0.744	-
Tamaki <i>et al</i> ^[50] , 2014	HCV	1046	76.8 - 70.8	Asia	119	0.61	> 3.25; > 3.25 + ΔFIB-4/ year ≥ 0.3; ΔFIB-4/ year ≥ 0.3
Ito <i>et al</i> ^[51] , 2015	HCV	516	135.6	Asia	60	-	2.0-4.0; > 4
Toyoda <i>et al</i> ^[52] , 2015	HCV SVR	522	86.4	Asia	18	-	> 2 (at SVR24)
Suh <i>et al</i> ^[47] , 2015	HBV	986	64.8	Asia	-	-	1.7-2.4; > 2.4
Suh <i>et al</i> ^[46] , 2015	ALD	6661	74.4	Asia	-	-	1.75 -2.1; > 2.1
Kim <i>et al</i> ^[36] , 2016	HBV	542	60	Asia	68	0.803	2.225
Fusco <i>et al</i> ^[53] , 2016	HBV, HCV, none	4492	96	Europe	22	-	3.25
Tseng <i>et al</i> ^[48] , 2017	HBV naive HBV NU	2075 (+532)	192.2	Asia	137 (+10)	0.75	1.29
Nishikawa <i>et al</i> ^[23] , 2017	HBV	338	60	Asia	33	0.768	3.666
Butt <i>et al</i> ^[54] , 2017	HCV	21116	12/36/60	United States	-	0.81 - 0.82	1.45
Kim <i>et al</i> ^[26] , 2018	ALD	924	36	Asia	83	0.69	3.5
Chang <i>et al</i> ^[25] , 2018	HCV no SVR	800	53.5	Asia	100	-	2.83
Peleg <i>et al</i> ^[55] , 2018	NAFLD	153	100	Israel	6	-	2.67
Song <i>et al</i> ^[27] , 2018	HBV	1014	46.8	Asia	37	-	1.45
Paik <i>et al</i> ^[16] , 2018	HBV	1006	61.2	Asia	36	0.71	1.45
Kanwal <i>et al</i> ^[45] , 2019	HCV SVR post-DAA	18076	43,8	United States	544	-	3.25; 1.45
Ioannou <i>et al</i> ^[56] , 2019	HCV SVR	48135	64.8	United States	1509	-	3.25
Alexander <i>et al</i> ^[57] , 2019	NAFLD	63971 (Fib-4 available)	39.6	Europe	-	-	2.67
Na <i>et al</i> ^[20] , 2019	HCV SVR	295	89.2	Asia	12	0.86 0.85	3.25 (pre-SVR); 2.5 (SVR)
Li <i>et al</i> ^[58] , 2019	HCV	711	-	Asia	249	0.961	2.18
Watanabe <i>et al</i> ^[59] , 2019	HCV SVR post-DAA	1174	17.9	Asia	35	-	4
Degasperi <i>et al</i> ^[60] , 2019	HCV SVR post-DAA	565	25	Europe	48	-	9
Kim <i>et al</i> ^[32] , 2020	HBV	444	84	Asia	25	0.753 (60 mo); 0.698 (84 mo)	3.25

HCC: Hepatocellular carcinoma; AUROC: Area under receiving operating characteristics curve; HIV: Human immunodeficiency virus; HCV: Hepatitis virus C; HBV: Hepatitis virus B; ALD: Alcoholic liver disease; Δ: Delta; SVR: Sustained virologic response; NU: Nucleoside analogues; NAFLD: Non-alcoholic fatty liver disease; DAA: Direct acting antiviral agents.

NAFLD^[61,62]. Nevertheless, since it seems to be the most widely validated score for predicting cirrhosis and HCC, we still support its use as general and simple screening for the risk of HCC during the everyday clinical practice in the main settings of the liver cirrhosis as HBV, HCV and NAFLD/NASH patients.

APRI and Fib-4 comparative studies

Several research groups performed comparative studies on the ability of APRI and Fib-4 in predicting HCC; most of them have reported that both Fib-4 and APRI may be used together as predictors of HCC development to improve their predictive accuracy and to overcome the above-mentioned limitations of each score. For example, Paik *et al*^[16] stratified more than 1000 HBV patients into three groups: those

with both APRI and Fib-4 above the proposed cut-off values, 0.5 and 1.45 respectively (Group 1), those with only one index above cut-offs (Group 2), and those with both indexes below (Group 3): They showed that hepatocellular carcinoma had highly different incidence rates in the 3 groups (13.9% in Group 1, 1.4% in Group 2, 1.2% in Group 3, $P < 0.001$); similarly, in the non-cirrhotic population the rates were 11.4% for Group 1, 1.5% for Group 2 and 0.4% for Group 3 ($P < 0.001$). This research suggested that the combined use of APRI and Fib-4 can be effective in stratifying the HCC risk and it may be preferred to the use of a single test^[61]. Besides, Na *et al*^[20] identified both APRI and Fib-4 as independent predictive tools for HCC in patients with chronic hepatitis C responsive to Interferon therapy. Indeed, the annual incidence of carcinoma was significantly higher in those patients with a post-treatment APRI 0.5 (1.67% *vs* 0.07%, $P < 0.0001$), as well as in those with a post-treatment Fib-4 ≥ 2.5 (1.49 *vs* 0.01, $P = 0.0003$). As regards to the HCV and the DAA setting, although a previous study^[29] on a small cohort of patients did not find at multivariate analysis a predictive role for Fib-4 and APRI, a recent larger evaluation in the above-mentioned study by Kanwal *et al*^[45] found that persistently high Fib-4 and APRI after HCV-eradication in both patients with and without cirrhosis was associated with an increased risk of HCC development.

Finally, a study by Peleg *et al*^[55] in NAFLD patients explored the accuracy of APRI and Fib-4 in predicting the development of various malignancies (including HCC): The results showed that, with adjustments for gender, age, hypertension and type 2 diabetes, an APRI score > 1.5 (HR 4.94, 95%CI: 1.92–12.82, $P = 0.0009$) and a Fib-4 score > 2.67 (HR 6.12, 95%CI: 2.31–16.17, $P = 0.0003$) were associated with the occurrence of malignancies. Thus, according to recent publications, both APRI and Fib-4 can have a potential utility in predicting primary HCC development, with increased accuracy when combined. However, further research should be carried out to confirm these data in all the different liver disease aetiologies and to better explore the role of APRI and to define its best cut-off values, even though in most of the above-mentioned studies the predictive accuracy remained rather low. On the other hand, stronger data are available for the use of Fib-4 in the setting of HBV also during NUC therapy, in NAFLD as general screening of HCC risk and in HCV before and after eradication for a predictor of the risk to select patients that require long term surveillance.

Forns index

The index developed by Forns *et al*^[63] in 2002, before the introduction of transient elastography techniques was first proposed as a non-invasive tool for the detection of patients with non-significant liver fibrosis. It is calculated using four variables (age, gamma glutamyl transferase levels, total cholesterol levels and platelet count), with the following formula: $7.811 - 3.131 \times \ln [\text{platelet count (109/L)}] + 0.781 \times \ln [\text{gamma glutamyl transferase (IU/L)}] + 3.467 \times \ln [\text{age (years)}] - 0.014 \times [\text{cholesterol (mg/dL)}]$. The first studies on Forns index (FI) highlighted its accuracy in identifying patients with different stages of fibrosis and cirrhosis^[63,64]. In recent years, some authors have also tried to evaluate the usefulness of this score for HCC prediction. A study by Toyoda *et al*^[21], conducted on HCV patients responsive to antiviral therapy, evaluated the efficacy of various fibrosis markers (FI, APRI and Fib-4) to detect patients with low risk of developing HCC after SVR. All three scores performed well, but pre-treatment FI seemed to be the most accurate one; patients with a FI < 5.34 had a significantly lower HCC incidence compared to those with values above 5.34 ($P = 0.0012$). Besides, no subjects with low FI developed HCC after SVR, whereas HCC occurred both in patients with low APRI (9 cases) and patients with low Fib-4 (5 cases). These results showed that baseline FI (calculated before antiviral therapy) may be used to detect patients who can end the HCC surveillance program after the eradication of HCV.

Other significant findings were reported by D'Ambrosio *et al*^[65], who carried out a prospective study on patients who achieved SVR after interferon therapy ($n = 38$); the univariate analysis showed that FI > 6.9 resulted as a risk factor for HCC development (HR 12.8, 95%CI: 1.14–143.9; $P = 0.039$).

FI has shown promising results, but its value needs to be confirmed by further studies, with a higher number of HCC cases and in other aetiologies than HCV. However, the overall feeling is that FI is still mainly used for fibrosis assessment and has not easily entered clinical practice perhaps because of its complexity since it includes the evaluation of serum cholesterol which is not routinely performed in all centers.

Lok index

The Lok index is a non-invasive tool introduced by an American research group^[66] as a predictor of cirrhosis development in patients with chronic hepatitis C. This index is

based on simple laboratory parameters and it is calculated with the following formula: $\text{Log odds (predicting cirrhosis)} = 5.56 - 0.0089 \times \text{platelet count (} 10^3/\text{mm}^3) + 1.26 \times \text{AST/ALT ratio} + 5.27 \times \text{INR}$. Recently, a potential role of Lok Index in predicting HCC development has been explored. A retrospective study by an Egyptian group^[67] analyzed the performances of eight different biochemical scores (King score, Fibro Q, AST-ALT ratio, APRI, Lok index, Goteborg University Cirrhosis Index, Fibro Alpha, and Biotechnology Research Center). The results showed a quite significant correlation between an increased Lok index (≥ 2.4) and HCC development (sensitivity = 57.1%, specificity = 65.7%, with an AUROC = 0.66); however, the prognostic accuracy of this score proved to be worse than other indexes, especially the Fibro Alpha and the Biotechnology Research Center (AUROC 0.91 and 0.93 respectively), and not sufficient to propose it as a valid predictive tool. Interesting results were also reported in the previously mentioned study by D'Ambrosio *et al*^[65], conducted on subjects who achieved SVR for HCV; the analysis showed that a post-SVR Lok index > 0.5 was correlated with an increased risk of developing HCC (HR 6.24, 95%CI: 1.03-37.6; $P = 0.046$); in the HCC population, 3 out of 5 patients had Lok index > 0.5 , whereas in the not-HCC cohort, only 5 out of 33 patients had Lok scores > 0.5 ($P = 0.05$). This study demonstrated that, in a subset of cirrhotic patients, the HCC risk remains high even after SVR, and this aspect may be detected using the Lok index, as well as the FI. Despite some promising results, at present the Lok score is predominantly used for the prediction of cirrhosis; further trials with larger cohorts are needed to deeper explore its role as an HCC predictor in the different liver disease cohorts beyond HCV.

Albumin-bilirubin and platelet count-albumin-bilirubin scores

Another biochemical index used in clinical practice is the albumin-bilirubin (ALBI) score, introduced by Johnson *et al*^[68] to evaluate liver function in patients with hepatocellular carcinoma. It was initially proposed as an alternative to the Child-Pugh score to overcome some of the known limitations, such as the inclusion of non-objective parameters (ascites, encephalopathy). The ALBI score is based on serum levels of albumin and total bilirubin and can be calculated with the following formula: $(\log_{10} \text{bilirubin } [\mu\text{mol/L}] \times 0.66) + (\text{albumin } [\text{g/L}] \times -0.0852)$. Johnson and colleagues also proposed to stratify ALBI values into three grades (ALBI ≤ -2.60 : Grade 1; ALBI > -2.60 and ≤ -1.39 : Grade 2, ALBI > -1.39 : Grade 3), that were associated to different outcomes^[68]. Subsequently, other studies highlighted the accuracy of the ALBI score in assessing the liver function in subjects with HCC undergoing resection or other treatments (transarterial chemoembolization, transarterial radioembolization, thermic ablation)^[69-72]. This score proved to be effective in predicting the patient's clinical outcome, especially in terms of hepatic decompensation (HD) and post-treatment survival. More recently, an Italian research group^[73] observed that, in a cohort of HCV patients treated with DAA therapy, an elevated ALBI score before DAA treatment was strongly correlated with the occurrence of HCC (HR: 2.35, 95%CI: 1.05-5.25, $P = 0.038$). According to Johnson's cut-offs^[68], subjects with ALBI grade 2 or 3 showed a significantly higher risk of developing HCC than those with ALBI grade 1 (HR 2.71, 95%CI: 1.08-6.83, $P = 0.01$).

A more recent study by Fujita *et al*^[74] evaluated the HCC-risk of 125 prospectively collected HCV patients, identifying 3 categories with different HCC-risk according to ALBI percentile distribution, which are from that at lower to higher risk: Q1 with ALBI score below -2.773, Q2 with ALBI score between -2.773 and -2.215 and Q3 with ALBI score above -2.215 at baseline ($P < 0.05$). More importantly, low ALBI scores at baseline inversely correlated with the HCC-free survival of the patient. Another model, the platelet count-albumin-bilirubin (PALBI) score, has been developed by integrating the platelet count, which acts as a surrogate for the degree of portal hypertension, into the ALBI score. This marker has proved to be a valid predictor of the overall survival among patients with HCC undergoing various treatments, such as resection, ablation or radiotherapy^[75-77]. Other authors^[78,79] have also reported that the PALBI score can be used to predict the outcome of both patients with decompensated cirrhosis and subjects with liver-related complications. However, at present, there is no available data about the application of the PALBI score in predicting the development of primary HCC. In conclusion, to date only a few studies evaluated the predictive role of ALBI score for HCC development and its use is limited as prognostic markers after HCC treatment; this could be due to the fact that this score provides an objective estimation of the hepatic reserve estimation not completely taking into account the carcinogenetic mechanisms related to advanced cirrhosis and portal hypertension. Moreover, ALBI scores variations are more likely in advanced stages of liver cirrhosis, when HCC is already expected.

Indocyanine green retention test

The indocyanine green retention test (ICG R15) is a widely-used method for the evaluation of hepatic function^[80,81]. This test is based on the intravenous injection of a contrast agent, the ICG, which is eliminated by the biliary system. Fifteen minutes after the injection, the agent's clearance is assessed: In subjects with preserved liver function, the retention rate of ICG is normally lower than 10%; a retention value above 10% indicates a reduced hepatic function. At present, this test plays a central role in the pre-operative assessment of HCC patients undergoing resection and helps surgeons plan the extent of hepatectomy.

Several studies^[82,83] highlighted that ICG R15 could be used to detect, among patients with compensated cirrhosis, those at higher risk of developing portal hypertension and esophageal varices. Therefore, this test was proposed as a non-invasive tool to identify patients who need endoscopic surveillance. The study by Lisotti *et al*^[84] underlined the correlation between high ICG R15 values and the occurrence of HD in subjects with cirrhosis and PH. It is worth mentioning that patients with an ICG R15 > 23% showed an HD incidence of 70% in the first 3 years after the evaluation; furthermore, 18 out of 134 patients developed an HCC during the follow-up period, while twelve of them had previously experienced at least one episode of HD.

Another study by Song *et al*^[85] showed that ICG R15 > 10% is an independent risk factor for HCC recurrence in patients who underwent resection; in fact, subjects with ICG R15 > 10% had lower recurrence-free survival rates than the rest of the population. However, in literature there is no experimental data focused on the performance of ICG R15 in predicting primary HCC even if promising data have been highlighted in the setting of HCC recurrence. However, multiple confounding factors are involved in ICG flow and metabolism^[86], and in addition, if compared to other available NITs it seems to be more inquiring, thus, we do not advise its routine use in HCC-risk assessment.

ULTRASOUND BASED NITs

Liver stiffness measurement

In recent years, the measurement of liver stiffness using transient elastography (FibroScan®; Echosens, Paris, France) has been used to assess the degree of hepatic fibrosis and thus to evaluate the risk of related complications^[87-89]. In the last decade, research was also focused on the correlation between LSM and HCC development. Studies reporting this correlation are reported in Table 3^[49,60,89-120]. Several cross-sectional trials^[89,110,117] demonstrated that the median values of liver stiffness in patients with HCC are significantly higher than in those without HCC.

One of these large prospective trial by Poynard *et al*^[96] ($n = 3927$) on chronic hepatitis C patients found that LSM was predictive of severe liver-related complications (AUROC 0.77; $P < 0.0001$), including primary HCC (AUROC 0.86; $P < 0.0001$). Other authors tried to quantify with LSM the risk of developing primary HCC after DAAs therapy. Rinaldi *et al*^[111] found that an LSM cut-off value of 27.8 kPa at baseline before treatment identified patients at high risk of HCC after DAA, whereas Corma-Gómez *et al*^[121] found in an HIV/HCV cohort treated with DAA that also Fib-4 in addition to LSM was associated with HCC occurrence. Another recent study^[60] carried out in patients undergoing DAA therapy found that baseline LSM > 30 kPa independently predicted de novo HCC, with a 3-year estimated incidence of 20% in these patients versus 5% in patients with LSM ≤ 30 kPa. In the same study, in a model without LSM but including LSM-spleen to platelet ratio score and Fib-4, the latter was found to be independently associated with de novo HCC occurrence.

Nevertheless, all these studies only highlighted this “static” phenomenon, without analyzing the “dynamic” correlation between the progression or regression of hepatic fibrosis and the risk of developing HCC. Because of this limitation, several longitudinal prospective studies have been recently conducted. The first one, published by a Japanese group on a large cohort of 866 subjects with chronic C hepatitis^[115], proved that an LSM value > 10 kPa is an accurate predictor of increased HCC risk (LSM values 10.1-15 kPa, HR 16.7; LSM 15.1-20, HR 20.9; LSM 20.1-25, HR 25.6; LSM > 25 kPa, HR 45.5; all with $P < 0.001$). In another prospective study carried out by Jung *et al*^[90] on HBV patients it was noticed that subjects with LSM > 8 kPa had an increased HCC risk, and that the incidence of HCC was directly proportional to LSM values: for LSM 8.1-13 kPa, HR 3.07 ($P = 0.047$); for LSM 13.1-18 kPa, HR 4.68 ($P = 0.012$); for LSM 18.1-23 kPa, HR 5.55 ($P = 0.009$); for LSM > 23 kPa, HR 6.60 ($P = 0.004$). After a median follow-up of 18 mo, a second LSM was made to evaluate if changes over time were related to a variation in HCC risk: Patients with baseline LSM ≤ 13 kPa and follow-up LSM > 13 kPa had a significantly higher incidence of HCC

Table 3 Studies reporting the role of transient elastography in predicting hepatocellular carcinoma

Ref.	Etiology	Patients (n)	Follow-up (mo)	Region	HCC (n)	AUROC	Cut-off (kPa)
Masuzaki <i>et al</i> ^[110] , 2008	HCV	265	-	Asia	85	0.805	25
Nahon <i>et al</i> ^[116] , 2009	HCV	265	-	Europe	66	-	-
Masuzaki <i>et al</i> ^[115] , 2009	HCV	866	36.0	Asia	77	-	25
Kuo <i>et al</i> ^[117] , 2010	HBV, HCV, non-B/non-C	435	-	Asia	106	0.736	24
Akima <i>et al</i> ^[118] , 2011	Mixed (HCV: 85%)	157	40.7	Asia	41	0.787	12.5
Jung <i>et al</i> ^[90] , 2011	HBV	1130	30.7	Asia	57	-	8
Fung <i>et al</i> ^[91] , 2011	HBV	528	35.0	Asia	7	-	10
Robic <i>et al</i> ^[94] , 2011	Mixed	100	24.0	Europe	4	0.837	21.1
Klibansky <i>et al</i> ^[95] , 2012	Mixed	667	28.7	USA	16	0.870	10.5
Chon <i>et al</i> ^[49] , 2012	HBV	1126	30.7	Asia	63	0.789	-
Kim <i>et al</i> ^[92] , 2012	HBV	128	27.8	Asia	13	0.722	19
Calvaruso <i>et al</i> ^[97] , 2012	HCV/HIV	275	32	Europe	-	-	14-40
Salmon <i>et al</i> ^[98] , 2012	HCV/HIV	244	30	Europe	21	-	12.5
Perez-Latorre <i>et al</i> ^[99] , 2013	HCV	60	42	Europe	7	0.77	25-40
Feier <i>et al</i> ^[89] , 2013	HCV	144	-	Europe	72	0.680	38.5
Wang <i>et al</i> ^[119] , 2013	HCV	198	47.8	Asia	10	-	12
Narita <i>et al</i> ^[120] , 2013	HCV	151	24.1	Asia	9	-	14
Kim <i>et al</i> ^[93] , 2013	HBV	162	24.0	Asia	12	0.736	12
Poynard <i>et al</i> ^[96] , 2014	HCV	3927	144	Europe	84	0.860	50
Wong <i>et al</i> ^[100] , 2014	HBV	1555	69	Asia	55	0.83	11
Kim <i>et al</i> ^[102] , 2015	HBV	2876	48.9	Asia	52	0.532	13
Wang <i>et al</i> ^[103] , 2016	HCV	278	91.2	Asia	18	0.781	12
Adler <i>et al</i> ^[105] , 2016	Mixed	432	31.3	Europe	41	-	20
Bihari <i>et al</i> ^[106] , 2016	HBV	964	-	Asia	14	0.767	-
Seo <i>et al</i> ^[107] , 2016	HBV	381	48.1	Asia	34	0.745	-
Jeon <i>et al</i> ^[104] , 2017	HBV	540	54.1	Asia	81	0.598	13
Li <i>et al</i> ^[101] , 2017	HBV	1200	48	Asia	156	-	-
D'Ambrosio <i>et al</i> ^[108] , 2018	HCV	404	36	Europe	24	-	-
Wang <i>et al</i> ^[109] , 2019	HBV	371	67.2	Asia	27	0.636	21.5
Degasperi <i>et al</i> ^[60] , 2019	HCV SVR	546	25	Europe	28	-	30
Rinaldi <i>et al</i> ^[111] , 2019	HCV SVR	258	24	Europe	35	0.691	27.8
Izumi <i>et al</i> ^[112] , 2019	HCV	419	30	Asia	32	0.806	8
Izumi <i>et al</i> ^[112] , 2019	HBV	377	27	Asia	23	0.795	6.2
Izumi <i>et al</i> ^[112] , 2019	NAFLD	258	30	Asia	33	0.698	5.4
Pons <i>et al</i> ^[113] , 2019	HCV SVR	572	33	Europe	25	-	-
Nakagomi <i>et al</i> ^[114] , 2019	HCV	1146	78	Asia	190	-	-

AUROC: Area under receiving operating characteristics curve; kPa: Kilopascal; HCV: Hepatitis virus C; HBV: Hepatitis virus B; HIV: Human immunodeficiency virus; SVR: Sustained virologic response; NAFLD: Non-alcoholic fatty liver disease.

than those with both values ≤ 13 kPa ($P < 0.001$); on the contrary, subjects with baseline LSM > 13 kPa who experienced regression of LSM below 13 kPa during follow-up had a significantly lower incidence of HCC than those who maintained an LSM value > 13 kPa ($P < 0.001$). Therefore, this study demonstrated that LSM can be also used as a “dynamic” predictor of HCC risk, since its changes over time cause variations in the probability of developing HCC. This dynamic aspect has also been studied by our research group, which evaluated liver stiffness in HCV patients before and after DAAs therapy^[122]. The results of our study showed that subjects who developed HCC had a lower reduction of LSM (Δ LS) than the rest of the cohort (-18.0% *vs* -28.9%, $P = 0.005$); a Δ LS $< 30\%$ resulted as an independent risk factor for HCC development at multivariate analysis. Another recent study on this topic, recently published by Pons *et al*^[113], found that LSM < 10 kPa (HR 0.33; 95%CI: 0.11-0.96) and albumin levels (HR 0.08; 95%CI: 0.02-0.25), both evaluated during follow-up, were independently associated with the risk of HCC; moreover, the group with a combination of these two predictors led to an HCC incidence ratio $\geq 1.9/100$ patient-

years.

LSM has also been compared with other NITs. Chon *et al.*^[49] compared the performance of LSM in predicting HCC with other indexes, such as LSPS, APRI and Fib-4; among all, LSM proved to be the most accurate model (AUROC 0.789).

Since the epidemiology of the liver disease is rapidly changing in the last decade due to the outbreak of new antiviral therapies and changing in the general population lifestyle, increased attention has been addressed to the evaluation of the prognostic significance of NITs in non-alcoholic fatty liver disease/steatohepatitis. A Japanese study^[112] including cACLD patients with different aetiologies found that in NAFLD patients the incidence of HCC development was significantly higher among those with $LSM \geq 5.4$ kPa and $CAP \leq 265$ dB/m than among others (HR 8.91, 95% CI: 1.47-67.97, $P = 0.0192$). A further study^[123] on NAFLD patients was not able to find a cut-off value for HCC prediction, even though the authors reported an increased incidence of HCC with increasing LSM (< 12 kPa: 0.32%; 12-18 kPa: 0.58%; 18-38 kPa 9.26% and > 38 kPa: 13.3%).

In conclusion, LSM is a good prognostic test, better than other liver fibrosis NITs, for HCC development prediction in chronic liver disease due to different aetiologies. Notably, a repeated assessment over time of LSM in cirrhotic patients could be more accurate than a single evaluation in monitoring the risk of HCC, even after viral eradication.

LSM-spleen to platelet ratio score

The LSM-spleen to platelet ratio score (LSPS) is a biochemical index obtained using the following formula: $LSM \text{ (kPa)} \times \text{spleen diameter (mm)} / \text{platelet count}$. This score was firstly proposed as a predictive tool for high-risk oesophageal varices in patients with HBV-related cirrhosis^[124], and thus also as a surrogate marker of portal hypertension. Subsequently, various authors^[49,125,126] have highlighted the relationship between an elevated LSPS and an increased risk of developing primary HCC. In a study by Shin *et al.*^[125] on 227 subjects with chronic HBV infection, the 18 patients who developed HCC averagely had higher LSM values, a longer spleen diameter and a lower platelet count than the rest of the study population (all $P < 0.05$). In addition, a LSPS of 1.1-2.5 was associated with a HR of 2.0 ($P = 0.032$) for HCC and a LSPS > 2.5 implied an HR of 8.7 ($P = 0.002$)^[125]. Other important results have been reported by Marzano *et al.*^[126], who enrolled HBV patients responsive to nucleot(s)ide analogues: Subjects with a post-therapy LSPS < 0.62 showed a significantly lower incidence of HCC compared to those with values ≥ 0.62 (7% *vs* 36%, $P = 0.001$)^[126]. Antiviral therapies generally lead to the regression of cirrhosis and to a lower incidence of complications in this kind of patients^[127]. The study also showed that low LSPS values at the end of the therapy were related to a lower risk of HCC occurrence, as well as to more significant regression of portal hypertension. In the previously mentioned study by Chon *et al.*^[49], various scores were evaluated as HCC predictors in patients with chronic hepatitis B: LSM and LSPS (AUROC = 0.789 and 0.788, respectively) showed better predictive performances than APRI, age-spleen-to-platelet ratio index, P2/MS, and Fib-4 (AUROC = 0.729, 0.756, 0.696, and 0.744, respectively). However, at multivariate analysis, LSM resulted as the only independent predictor of HCC (HR = 1.040, $P = 0.006$), whereas LSPS was not significant (HR 1.002, $P < 0.05$). Therefore, these good results on LSPS could be explained by the ability of both LSM and spleen to platelet score to evaluate either the degree liver fibrosis and the additional carcinogenetic mechanisms added by portal hypertension in advanced chronic liver disease. However, further validation studies of these scores are still needed.

Spleen stiffness measurement

During the last decade, the use of transient elastography has been extended to the measurement of spleen stiffness. This organ, differently from the liver, is involved in the hemodynamic modifications due to PH even at higher values of portal pressure. The level of spleen stiffness (SS) is, therefore strictly related to the degree of PH even for HVPG values above 10-12 mmHg^[128,129]. Several studies highlighted an excellent correlation between SS measurement (SSM) and the degree of PH assessed by HVPG^[130,131]. Several reasons could explain this phenomenon. Firstly, the position of the organ allows a downstream of the portal circle, the elevation of portal pressure causes a blood reflow through the splenic vein, which leads to spleen's congestion; secondly, the abnormal portal pressure induces structural modifications of the spleen (such as hypertrophy of the red pulp) as well as the development of a hyperdynamic circulation, both factors that play a role in the increase of spleen stiffness^[132-134]. Recent studies^[135-137] have shown the excellent performance of SSM in predicting the presence of oesophageal varices^[138-142] and the risk of cirrhosis-related complications. Colecchia *et al.*^[135] conducted a prospective study including patients with compensated cirrhosis finding that $SSM > 54$ kPa was able to predict the development of HD during follow-

up, including ascites, variceal bleeding, encephalopathy and HCC. In the HCC setting, the same group^[143] found that an SSM > 70 kPa was the only independent predictor of late HCC recurrence (more than 24 mo) after resection of primary HCC. The correlation between increased SSM and the development of HCC is probably based on the role of portal hypertension. Indeed, it has been demonstrated that PH causes alterations in the portal circle, such as intrahepatic shunts, veno-occlusive thrombotic lesions and sinusoidal capillarization, which lead to lower sinusoidal perfusion^[144]. This local ischaemic condition may cause the production of HIF (hypoxia-induced factor) and other cytokines, which stimulate neo-angiogenesis and fibrogenesis in dysplastic nodules^[145]; the proliferation of new blood vessels and the progression of fibrosis favour the carcinogenesis process. Thus, SSM can be considered a promising method, with better performances than LSM in assessing the PH degree. However, to date, no studies directly evaluated the role of SSM in predicting primary HCC.

CONCLUSION

Several prognostic models based on NITs have recently been proposed as HCC predictors in experimental trials. However, the evidence that non-invasive tests can easily and accurately predict the risk of developing hepatocellular carcinoma in clinical practice is still scarce.

The most reliable data is available on LSM which accurately reflects the severity of the liver disease. LSM is able to evaluate either liver fibrosis degree, inflammation and portal hypertension, which are the main pathogenetic players of HCC development and risk. Furthermore, LSM can be used dynamically for monitoring HCC risk over time in cirrhotic patients. However, more studies are needed to validate LSM results on different aetiologies, such as NAFLD, and to determine specific optimal cut-off, able to assess HCC risk for each etiology. Moreover, the predictive role of other NITs should be further investigated. Despite these limitations, NITs represent valid tools helping clinicians in their daily practice, and they soon may also play a role in implementing surveillance strategies for HCC.

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