# PREDICTIVE SCORES FOR HEPATOCELLULAR CARCINOMA OCCURRENCE AFTER HEPATITIS C VIRUS CURE WITH DIRECT ANTIVIRALS

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PREDICTIVE SCORES FOR HEPATOCELLULAR CARCINOMA OCCURRENCE AFTER HEPATITIS C VIRUS CURE WITH DIRECT ANTIVIRALS (Abstract): Hepatitis C virus (HCV) chronic infection has an important tumorigenic propensity and represents a major cause of hepatocellular carcinoma (HCC). Although the therapy of chronic HCV infection has been revolutionized with the introduction of direct acting antivirals (DAAs) resulting in sustained virological response (SVR) in up to 98% of patients, viral clearance does not totally alleviate the risk of liver-related complications, including HCC. The **aim** of our study was to assess the performance of predictive scores for HCC occurrence in patients with chronic HCV infection who obtained SVR with DAAs. **Material and methods:** We conducted a prospective study in which we included 992 patients diagnosed with chronic HCV infection and treated with DAAs, between 1st November 2015 and 31st December 2020. HCC risk scoring systems were applied to each patient enrolled in the study before starting DAA treatment. HCC was diagnosed by imaging methods such as computed tomography and magnetic resonance imaging. **Results:** Of the 992 patients included in the study, 59 (5.9%) were diagnosed with HCC during the follow-up period, mostly women (55.9%) with a mean age of 60-69 years. The mean time to HCC onset was 19.53 ± 11.553 months, with a median of 17 months, with a cumulative incidence at 1, 3, and 5 years of 1.1%, 2.1%, and 2.9%, respectively. The General Evaluation Score (GES), aMAP and ADRESS score had statistically significant higher values in patients with HCC than in those without HCC. GES demonstrated a good discriminating power with an AUC coefficient of 0.804 at a cut-off value of 6.25 which has good sensitivity and specificity (0.746 and 0.799, respectively). **Conclusions:** GES score has a very good predictive power for the risk of HCC after obtaining SVR and could be recommended in clinical practice. Future development and validation of other individualized predictive scores score is needed for a correct and cost-efficient selection of patients with high risk of HCC. **Keywords:** CHRONIC HEPATITIS C INFECTION, DIRECT-ACTING ANTIVIRALS THERAPY, HEPATO-CELLULAR CARCINOMA, PREDICTIVE SCORES.

Hepatitis C virus (HCV) chronic infection has an important tumorigenic propensity and represents a major cause of hepatocellular carcinoma (HCC). Although the therapy of chronic HCV infection management has been revolutionized with the introduction of direct acting antivirals (DAAs), resulting in sustained virological response (SVR) in up to 98% of patients, viral clearance does not totally alleviate the risk of liver-related complications, including HCC (1). Still, there is strong evidence that SVR significantly improves the prognosis in patients with chronic HCV infection by lowering the risk of liver cirrhosis, decompensation and HCC, irrespective of whether it was achieved by using interferon-based regimens or DAAs (2). The high efficacy and availability of DAAs worldwide determined a rapidly growing of the SVR-patients pool, and thus it seems reasonable to consider strategies for a correct stratification of HCC risk.

The main tools for early diagnosis of HCC are screening strategies, which should accomplish the main goal of cancer surveillance that is the decrease of cancer specific mortality at cost-effective terms (3). In line with this, the current guidelines have different recommendations for HCC surveillance in those with SVR. The European Association for the Study of the Liver (EASL) considers the presence of F3 fibrosis and cirrhosis before start of treatment as an indication for HCC surveillance (4), whereas the American Association for the Study of Liver Disease (AASLD) takes into account only those with cirrhosis (5). Interestingly, the recommendations from the Asian Pacific Association for the Study of the Liver does not rely on fibrosis stages and recommends HCC surveillance in all patients with SVR (6). However, it is important to take into consideration the cost-effectiveness of HCC surveillance which is mainly determined by an accurate estimation of the incidence and thus by a correct stratification of HCC risk after SVR. There are numerous studies that evaluated several stratification tools regarding HCC risk in patients with HCV clearance, but data is still scarce (7,8).

In this study, we aimed to assess the performance of several predictive scores for HCC occurrence in patients with chronic HCV infection who obtained SVR with DAAs.

## MATERIAL AND METHODS

*Study design and study population*

We conducted a prospective study in which we included 992 patients diagnosed with chronic HCV infection and treated at the Institute of Gastroenterology and Hepatology in Iasi, between 1st November 2015 and 31st December 2020. All patients met the following inclusion criteria: (1) age over 18 years; (2) diagnosis of HCV infection with detectable HCV-RNA; (3) no contraindication of DAAs therapy; (3) without previous diagnosis of HCC. All patients from the study cohort were followed up until February 1st , 2022.

*Clinical and laboratory data*

Patients enrolled in the study were followed-up prospectively by clinical-biological and imaging monitoring from study inclusion until 1st February 2022. Demographic variables for the enrolled study population included age and sex. Cirrhosis was defined as the presence of any of the following findings: coarse liver echotexture and nodular liver surface by ultrasonography, clinical features of portal hypertension (e.g., ascites, splenomegaly, or varices), or thrombocytopenia (<150,000/mm3).

Laboratory data included anti-HCV, aspartate and alanine aminotransferases, bilirubin, alkaline phosphatase, Gama glutamyl transpeptidase, albumin, international normalized ratio, prothrombin time, serum creatinine, hemoglobin, platelet count, and alpha-fetoprotein levels. Serum HCV RNA levels were measured in all patients before and at 3 months after the end of treatment (COBAS TaqMan HCV quantitative test (Roche Molecular Systems, Inc. Branchburg, NJ). Transient elastography (FibroScan; Echosens, Paris, France) was used to perform the liver stiffness measurement (LSM) with 13 kPa as the cutoff point for cirrhosis.

*Diagnosis of HCC*

The diagnosis of HCC was established based on current guideline recommendations using abdominal US as the initial method (4). In case of ultrasound detection of a nodule larger than 1 cm, the diagnosis was confirmed by a more sensitive method such as CT or MRI, and if the result was inconclusive, the following imaging method was used, liver biopsy being reserved for cases uncertain at 2 successive investigations.

*Predictive scores*

HCC risk scoring systems were applied to each patient enrolled in the study before starting DAA treatment.

The General Evaluation Score (GES) comprises 5 variables scored each as follows: (1) gender: women 0 points, men 3.5 points; (2) age: ≤54 years 0 points, >54 years 1 point; (3) degree of fibrosis: F3 1.5 points, F4 3 points; (4) albumin: ≥ 3.8g/dL 0 points, <3.8g/dL 2 points; (5) AFP: ≤20 ng/ml 0 points, > 20 ng/ml 3 points. The total score can reach a maximum value of 12.5 points and allows placing the patient in one of 3 risk groups: low ≤6, intermediate risk >6 - 7.5, and high risk >7.5.

The aMAP score was calculated using the formula ({0.06 x age + 0.89 x sex (male:1, female: 0) + 0.48 x [(log10 bilirubin x 0.66) + (albumin x −0.085)] - 0.01 x platelet count} + 7.4) / 14.77 x 100. Based on the score, the patients were divided into 3 groups: low risk < 50 points, intermediate between 50 and 60 points, high > 60 points.

The ADRESS-HCC score was calculated based age, presence of type 2 diabetes, race, etiology of cirrhosis, sex and severity of liver disease. Depending on the score obtained, patients were divided into 3 groups: low risk (corresponding to quartile 1), intermediate (quartile 2-3) and high (quartile 4).

Statistical processing was carried out using *Microsoft Excel* and *SPSS version 28* (Inc., Chicago, IL) software. Survival curves were estimated by the Kaplan-Meier method and compared, for univariate analysis, by the log rank test. To evaluate the discriminatory ability for the prediction of HCC, we evaluated the accuracy of prediction for each scoring system. This point was evaluated calculating the area under the receiver operating characteristic (ROC) curve for each staging system.

The study was carried out in accordance with the ethical principles of the Declaration of Helsinki, the protocol being explained in detail to all patients. Informed consent for participation in the study was obtained from all patients and/or their relatives.

## RESULTS

Of the 992 patients included in the study, 59 (5.9%) were diagnosed with HCC during the follow-up period, mostly women (55.9%) with a mean age of 60-69 years. The mean time to HCC onset was 19.53 ±

11.553 months, with a median of 17 months; the shortest period of time was 3 months and the longest 51 months. Of the total of 59 patients with HCC, only 6 of them (10.2%) were diagnosed within an interval shorter than 6 months, in the remaining 53 (89.8%) the diagnosis was established after more than six months. Thus, the cumulative incidence at 1, 3, and 5 years was 1.1%, 2.1%, and 2.9%, respectively.

According to the GES score, the vast majority of patients were in the low-risk class (76.6%), followed by the intermediate-risk class (14.5%), the fewest being in the high-risk class (8, 9%) (fig. 1). On the other hand, according to the aMAP interpretation, 60.7% of the patients were in the high-risk category, 33.5% in the intermediate risk category, and only 5.7% of the patients belonged to the low-risk category (fig. 2). Regarding the ADRESS score, 25% of patients had values less than 5.0565 (Q1), 50% had < 5.5557 (Q2) and 25% had > 5.9608 (Q3) (fig. 3).

The comparative analysis of GES, aMAP and ADRESS risk scores in patients with HCC versus those without HCC showed that the score values were significantly higher in patients with HCC (fig. 4).

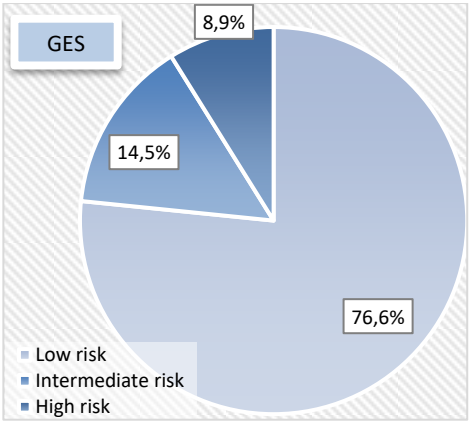


**Fig. 1**. Risk classes according to GES

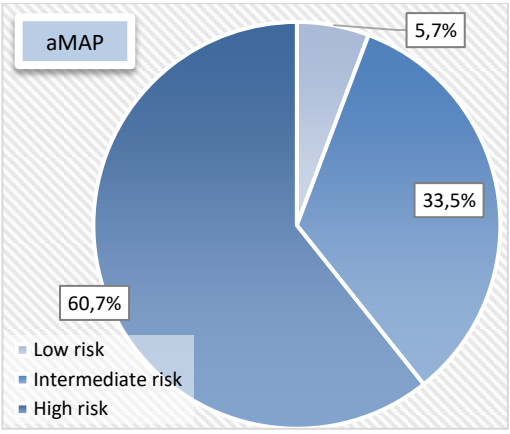


**Fig. 2.** Risk classes according to aMAP

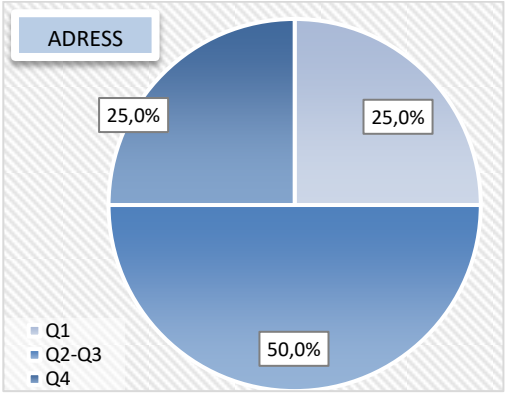


**Fig. 3**. Risk classes according to ADRESS

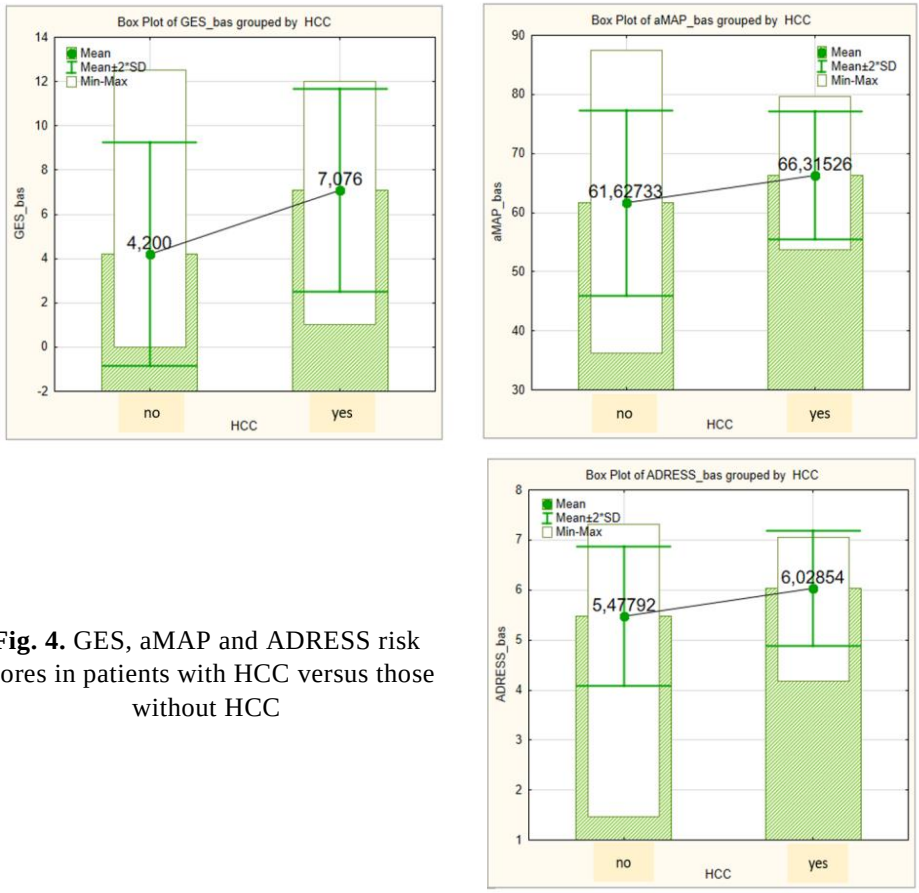


**Fig. 4.** GES, aMAP and ADRESS risk scores in patients with HCC versus those without HCC

Next, we performed the ROC analysis of the prediction scores, with the aim of identifying their discrimination potential (by evaluating the AUC surface) and the optimal cut-off values (with the best sensitivity-specificity combination) (tab. I).

TABLE I.

**ROC analysis of the prediction scores for HCC**

| | AUC (Area under Curve) | p | Confidence interval 95% | | Cut-off value | Sensitivity | Specificity |
|---|---|---|---|---|---|---|---|
| | | | Lower limit | Upper limit | | | |
| **GES** | 0.804 | 0.000 | 0.748 | 0.860 | 6.25 | 0.746 | 0.799 |
| **aMAP** | 0.700 | 0.000 | 0.638 | 0.761 | 64.57854 | 0.737 | 0.650 |
| **ADRESS** | 0.743 | 0.000 | 0.681 | 0.805 | 5.6571 | 0.797 | 0.599 |

Only GES had the AUC coefficient greater than or equal to 0.8 - which corresponds to a good or excellent discriminating power for the investigated situation, namely the risk of HCC. The identified cut-off value of 6.25 has both reasonably good sensitivity and specificity. The corresponding ROC curve is illustrated in figure 5.

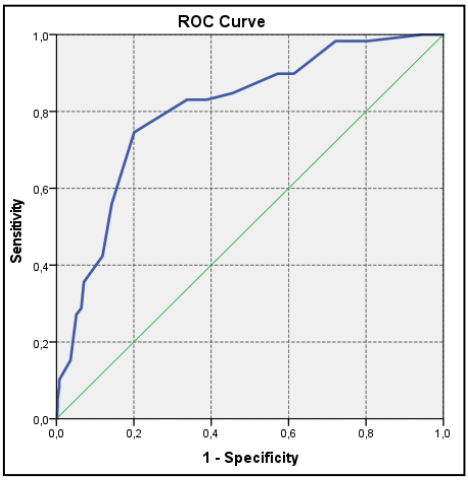


**Fig. 5.** ROC curve for GES

**DISCUSSION**

HCC risk scoring systems in patients with chronic HCV hepatitis are derived from prediction models used for chronic HBV hepatitis. Interest in these predictive systems has increased with the introduction of the new DAAs into the therapeutic management of patients with chronic HCV infection. In the pre-DAA era, when limited therapeutic options were reflected in the proportion of viremic patients, scoring systems were developed to expand or narrow the surveillance indications for HCC.

Research in recent years that identified the major risk factors involved in the occurrence of HCC, led to the development of numerous predictive scores, some externally validated and with a very good predictive value, such as the GES score, aMAP and ADRESS. Consequently, one of the aims of this study was to determine the effectiveness of these scores in predicting the risk of HCC after achieving SVR with AAD. Of the 3 scores, only the GES score had excellent discriminatory power for HCC risk at a cut-off value of 6.25 (AUC coefficient: 0.804). Indeed, the GES score was the only one of the 3 whose derivation cohort consisted of patients with chronic HCV infection treated with DAAs (9). However, in contrast to our results, the performance of the GES score was suboptimal in another recent study including 577 patients with HCV infection and liver cirrhosis who achieved SVR with the new DAAs (10). The authors' conclusions were that the GES score failed to correctly discriminate HCC risk, one of the reasons being that the demographic characteristics of the Caucasian patients included in this cohort are different from those of the Egyptian patients in the derivation cohort. However, it should be kept in mind that the results of this study are limited by the small number of patients included.

The aMAP and ADRESS scores, on the other hand, were derived from cohorts of patients with hepatopathies of various etiologies (11,12). The results in the case of the ADRESS score were more satisfactory compared to the aMAP score, but it did not have a good enough discrimination ability to accurately predict the risk of HCC ac-

cording to the 3 risk groups (the AUC coefficient in the case of the ADRESS was 0.743 versus 0.700 in the case of aMAP). Similarly, in a recent study conducted by Shiha *et al.*, the aMAP score failed to predict the risk of HCC in 2085 patients with chronic HCV genotype 4 infection and fibrosis grade F3 and F4 after achieving SVR with AAD (13).

In contrast, other studies evaluated composite HCC risk scores, which were based on combinations of multiple variables, to stratify patients into different HCC risk classes. Four studies focused only on patients with advanced fibrosis or cirrhosis, by proposing a combination of patient-related (age, sex, presence of DM) and biochemical (albumin, GGT, platelet count, AFP) variables, together with data related to by the severity of the liver disease (14,15). Abe *et al.* recently reported that the risk factors for HCC identified in multivariate analysis were pre-SVR serum albumin level for non-cirrhotic chronic HCV infection patients and ALBI score, platelet count and DM for CH patients (14).

## CONCLUSIONS

Our study showed that GES score has a very good predictive power regarding the risk of HCC after obtaining SVR and could be recommended in clinical practice for the identification of high-risk patients suitable for surveillance. Future development and validation of other individualized predictive scores score is needed for a correct and cost-efficient selection of patients with high risk of HCC.

## CONFLICT OF INTEREST AND FUNDING

The authors declare no conflict of interest.

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## REFERENCES

1. Cheng TS, Liang PC, Huang CF, *et al.* Real-world effectiveness of direct-acting antiviral agents for chronic hepatitis C patients with genotype-2 infection after completed treatment. *Kaohsiung J Med Sci* 2021; 37: 334-345.
2. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *J Hepatol* 2017; 5: S0168-8278(17)32273-0.
3. Akuta N, Sezaki H, Fujiyama S, *et al.* Simple Predictive Markers and Clinicopathological Features of Primary Liver Cancer following HCV Clearance with Direct-Acting Antivirals. *Oncology* 2023; 101(2): 79-88.
4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018; 69: 182-236.
5. Marrero JA, Kulik LM, Sirlin CB, *et al.* Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018; 68: 723-750.

6. Kanda T, Lau GK, Wei L, *et al.* APASL HCV guidelines of virus-eradicated patients by DAA on how to monitor HCC occurrence and HBV reactivation. *Hepatol Int* 2019; 13: 649-661.
7. Luna-Cuadros MA, Chen HW, Hanif H, Ali MJ, Khan MM, Lau DT. Risk of hepatocellular carcinoma after hepatitis C virus cure. *World J Gastroenterol* 2022; 28: 96-107.
8. Yamashita Y, Joshita S, Sugiura A, *et al.* aMAP score prediction of hepatocellular carcinoma occurrence and incidencefree rate after a sustained virologic response in chronic hepatitis C. *Hepatol Res* 2021; 51: 933-942.
9. Shiha G, Waked I, Soliman R, *et al.* GES: A validated simple score to predict the risk of HCC in patients with HCV-GT4-associated advanced liver fibrosis after oral antivirals. *Liver Int* 2020; 40(11): 2828-2833.
10. Bergna I, Degasperi E, D'Ambrosio R. Suboptimal accuracy of GES score to stratify post-SVR HCC risk in a single center cohort of European cirrhotics infected with any HCV genotype. *Liver Int* 2021; 41: 1152-1153.
11. Flemming JA, Yang JD, Vittinghoff E, Kim WR, Terrault N. Risk prediction of hepatocellular carcinoma in patients with cirrhosis: the ADRESS-HCC risk model. *Cancer* 2014; 120(22): 3485-3493.
12. Fan R, Papatheodoridis G, Sun J, *et al.* aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. *J Hepatol* 2020; 73(6): 1368-1378.
13. Shiha G, Mikhail N, Soliman R. External validation of aMAP risk score in chronic hepatitis C genotype 4 patients with liver cirrhosis who achieved SVR following DAAs. *J Hepatol* 2021; 74: 994-996.
14. Abe K, Wakabayashi H, Nakayama H, *et al.* Factors associated with hepatocellular carcinoma occurrence after HCV eradication in patients without cirrhosis or with compensated cirrhosis. *PLoS One* 2020;15(12):e0243473.
15. Alonso Lopez S, Manzano ML, Gea F, *et al.* A model based on non-invasive markers predicts very low hepatocellular carcinoma risk after viral response in hepatitis C virus - advanced fibrosis. *Hepatology* 2020; 72: 1924-1934.