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Prediction of Hepatocellular Carcinoma in a Portuguese Population after Hepatitis C Cure: Comparative Accuracy of Noninvasive Tests (Transient Elastography, FIB-4, and aMAP)

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Keywords
Chronic hepatitis C · Hepatocellular carcinoma · Risk assessment · Screening · Sustained virologic response

Abstract

Introduction: Chronic infection with hepatitis C virus (HCV) causes 25% of hepatocellular carcinoma (HCC) cases worldwide, a major cause of morbimortality even after sustained virologic response (SVR). Universal screening to all patients with advanced liver fibrosis is currently recommended. A risk-based strategy could improve the detection rate of early HCC and diminish the surveillance burden. Although several risk prediction models exist, exclusion of a subgroup of patients from surveillance has not yet been recommended. The objective of this study was the comparison of the predictive accuracy of transient elastography, FIB-4, and aMAP for HCC in HCV patients after SVR in Portugal. ***Methods:*** This was a multicentric

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retrospective study including patients with HCV after SVR. Comparative, univariate, multivariate, area under the ROC (receiver-operating characteristic) curve (AUC), and Youden's J-statistic analysis were performed. ***Results:*** HCC incidence was 4.2% (1.3/100 patient-years) after a median follow-up of 31 months with inclusion of 337 patients. All patients had a liver stiffness measurement (LSM) before SVR (considered the baseline), but only 148 (43.9%) had a transient elastography after SVR. FIB-4 and aMAP post-SVR were calculated in all patients. Multiple parameters positively correlated with HCC, but only age and baseline transient elastography remained as independent predictors in the multivariate analysis. The optimal cutoffs for prediction of HCC were baseline transient elastography 13.7 kPa, post-SVR transient elastography 16.5 and 15.8 kPa (first and last measurements, respectively), FIB-4 1.6, and aMAP 58. Baseline transient elastography revealed a fair accuracy in predicting HCC (AUC 0.776, $p < 0.001$), with the cutoff of 13.7 kPa presenting a sensitivity of 85% and a specificity of 69%. Regarding patients who were F3–4 at baseline ($n = 162$), almost one-third had a baseline LSM ≤13.7 kPa ($n = 51$, 31.5%), an FIB-4 ≤1.6 ($n = 50$, 30.9%), and an aMAP score ≤58 ($n = 48$, 29.6%), and these cutoffs presented an NPV of 98%, 94%, and 96%, respectively, when considering HCC development. ***Conclusion:*** Transient elastography (FibroScan) before SVR was a fair predictor of HCC, being more accurate than FIB-4 and aMAP. Transient elastography values ≤13.7 kPa at baseline, FIB-4 ≤1.6 and aMAP ≤58 were the cutoffs considered of low risk for HCC in a Portuguese cohort of HCV patients after SVR with advanced fibrosis. aMAP score is a risk-based surveillance tool that could improve the current HCC screening strategy, but further validation is needed.

Predição de Carcinoma Hepatocelular numa População Portuguesa após Cura de Hepatite C: Comparação da Precisão de Testes Não Invasivos (Elastografia Hepática Transitória, FIB-4, e aMAP)

Palavras Chave
Avaliação de risco · Carcinoma hepatocelular · Hepatite C crónica · Rastreio · Resposta virológica sustentada

Resumo

Introdução: A infeção crónica pelo vírus da hepatite C (VHC) causa 25% dos casos de carcinoma hepatocelular (CHC) em todo o mundo, uma causa major de morbi-mortalidade mesmo após a resposta virológica sustentada (RVS). Um rastreio universal a todos os doentes com fibrose hepática avançada é atualmente recomendado. Uma estratégia com base no risco poderia melhorar a taxa de deteção do CHC precoce e diminuir a carga do rastreio. Apesar de existirem diversos modelos de predição de risco, a exclusão de um subgrupo de doentes do rastreio ainda não foi recomendada. O objetivo deste estudo foi a comparação da capacidade preditiva da elastografia hepática transitória, FIB-4, e aMAP de CHC em doentes com infeção VHC após atingimento de RVS em Portugal. ***Métodos:*** Estudo multicêntrico retrospetivo que incluiu doentes com VHC após RVS. Foram realizadas análises comparativa, univariada, multivariada, área sob a curva ROC (AUC), e estatística J de Youden. ***Resultados:*** A incidência de CHC foi 4.2% (1.3/100 doente-anos) após um seguimento mediano de 31 meses com inclusão de 337 doentes. Todos os doentes incluídos apresentavam uma medição da rigidez hepática antes do atingimento da RVS (considerada a medição basal), mas a elastografia hepática transitória apenas foi repetida após a RVS em 148 doentes (43.9%). Os valores do FIB-4 e do aMAP no contexto pós-RVS foram possíveis de calcular em todos os doentes. Múltiplos parâmetros correlacionaram-se positivamente com o CHC, mas apenas a idade e a elastografia hepática transitória basal permaneceram como preditores independentes na análise multivariada. Os limiares ótimos para predição de CHC foram elastografia hepática transitória basal 13.7 kPa, elastografia hepática transitória basal pós-RVS 16.5 e 15.8 kPa (primeira e última medição, respetivamente), FIB-4 1.6 e aMAP 58. A elastografia hepática transitória revelou uma precisão razoável na predição de CHC (AUC 0.776, $p < 0.001$), com o limiar de 13.7 kPa a apresentar sensibilidade de 85% e especificidade de 69%. Relativamente aos doentes F3-F4 antes da RVS ($n = 162$), praticamente um terço apresentava uma elastografia hepática transitória basal ≤13.7 kPa ($n = 51$, 31.5%), score FIB-4 ≤1.6 ($n = 50$, 30.9%), e score aMAP ≤58 ($n = 48$, 29.6%), e estes limiares apresentaram um VPN de 98%, 94% e 96%, respetivamente, relativamente ao desenvolvimento de CHC. ***Conclusão:*** A elastografia hepática transitória (FibroScan) pré-RVS foi um preditor razoável de CHC, sendo mais preciso que o FIB-4 e o aMAP. Valores basais de elastografia hepática transitória ≤13.7 kPa, FIB-4 ≤1.6, e aMAP ≤58 foram os limiares considerados de baixo risco para CHC numa coorte de doentes Portugueses com VHC após RVS com fibrose avançada. O score aMAP é uma ferramenta de rastreio de CHC baseada no risco que poderá melhorar a estratégia atual, mas é necessária validação adicional.

Introduction

Hepatocellular carcinoma (HCC) is a major cause of morbimortality in patients with chronic hepatitis C who have achieved sustained virologic response (SVR) [1–3]. Approximately 25% of HCC cases worldwide are caused by hepatitis C virus (HCV) [4–7]. Timely detection of HCC is crucial for the potential reduction of mortality, since the success of treatment tremendously depends on an early stage at diagnosis [3, 4]. A risk-based surveillance strategy that permits an early diagnosis depends on the availability of a simple tool that stratifies patients according to their personal risk of HCC, in order to individualize screening accordingly [3, 4, 8–11].

The screening strategy currently recommended does not consider the individual risk of HCC, since it consists in performing a 6-monthly liver ultrasound to all at-risk patients, associated or not with the serum alpha-fetoprotein (AFP) [1, 10, 11]. Cirrhotic patients are the primary target since most cases of HCC develop in this population [4, 7–10]. Patients with advanced fibrosis maintain a significant residual risk of HCC after SVR, with an incidence that can reach 3.6/100 patient-years [1, 4, 7, 9, 10, 12, 13]. Various risk factors have been reported among HCV patients, but our current screening strategy depends entirely on the presumed histological stage of the liver disease, since it is usually assessed with noninvasive tests such as transient elastography (TE) [3, 5, 12–14].

Liver ultrasound as a screening tool for HCC has a low sensitivity for the detection of early HCC, even if complemented with AFP (composed sensitivity of 63%) [8, 11]. Therefore, there is a clear potential benefit in shifting to a more sensitive screening test in patients at a higher risk of HCC, in order to offer early diagnosis and improve prognosis [1, 8–10]. Simple algorithms based on age, blood tests, and liver stiffness measurement (LSM) identify a large proportion of patients who are at a very low risk of HCC development and thus might not benefit from surveillance [1]. Several risk prediction models have been proposed, but no recommendation regarding the identification of a group in whom surveillance is not warranted has been issued [1, 3, 4, 8].

TE is a widely used tool for noninvasive assessment of liver fibrosis. Liver stiffness is independently associated with HCC risk, even in patients without cirrhosis [14–16]. An LSM >10 kilopascal (kPa) categorizes HCV patients as having advanced fibrosis or cirrhosis, and guidelines recommend ongoing surveillance even in F3 patients [9, 10, 13]. Patients with LSM <17.5 kPa before antiviral treatment do not seem to benefit from HCC screening on the first 3 years after SVR in the absence of other risk factors [15]. In several prospective studies, the annual risk of HCC in HCV was very low for LSM ≤10 kPa, but reached 14.4% for values >25 kPa [9, 14]. Hence, it can be useful to repeat TE after SVR in order to more accurately stratify the residual risk of HCC [13]. However, cutoffs of LSM used in patients with untreated HCV are not validated in the post-SVR context, and HCC surveillance should be continued irrespective of the results of noninvasive tests post-SVR [13].

Fibrosis-4 (FIB-4) score is a noninvasive prediction tool of liver fibrosis that is already validated for several etiologies [17]. An elevated score also seems to be a particularly accurate predictor of the risk of HCC [6, 9]. Other noninvasive liver fibrosis scores have been studied in the context of HCV, but all performed worse than FIB-4 regarding HCC prediction [6].

The aMAP (age-male-ALBI-platelets) score is a recently developed model that estimates HCC risk in patients with chronic hepatitis [3, 18]. Scores <50 are considered of low risk, while patients who are classified in the high-risk group (aMAP >60) should undergo intensive surveillance to detect early HCC [3, 9]. The authors assessed and compared the predictive accuracy of TE, FIB-4, and aMAP for HCC and liver-related death in chronic hepatitis C after SVR in a Portuguese population.

Materials and Methods

All patients with chronic hepatitis C achieving SVR at eight Portuguese centers (Unidade Local de Saúde [ULS] Lisboa Ocidental [ULSLO], ULS Santa Maria [ULSSM], ULS Trás-os-Montes e Alto Douro [ULSTMAD], ULS de Almada-Seixal [ULSAS], ULS São José [ULSSJ], ULS de Loures-Odivelas [ULSLOD], ULS da Arrábida [ULSA], and ULS da Região de Leiria [ULSRL]) between June 2014 and June 2019 were screened for eligibility for this retrospective study. Exclusion criteria included previous liver transplantation and/or liver cancer, an HCC diagnosis on the first year after the start of antiviral therapy, or lack of a valid LSM available on the first 2 years before antiviral treatment.

Chronic HCV infection was diagnosed based on serum anti-HCV antibodies and HCV RNA positive for 6 months or longer. Liver cirrhosis was diagnosed by liver biopsy or by combining clinical, biochemical, and imagiological findings. HCC surveillance was conducted by liver ultrasound, computed tomography, or magnetic resonance imaging on a 6-monthly basis, associated or not with AFP, in all patients with advanced fibrosis [10]. If no advanced fibrosis, HCC surveillance was performed at the discretion of the physician.

The surveillance interval for HCC prediction started after the beginning of antiviral therapy. The end of follow-up was the date of the diagnosis of HCC, the last visit, liver transplantation, death, hospital discharge, transfer to another institution, or June 30, 2023, whichever came first. HCC diagnoses were confirmed by liver biopsy or relied on typical findings in computed tomography/magnetic resonance imaging in patients with cirrhosis.

Vibration-controlled TE (FibroScan) was used for LSM. LSM was assessed before SVR in all patients (baseline) and it was reassessed after SVR in a subgroup of patients. When more than two LSM values post-SVR were available, only the most recent and the last values were considered. The final value corresponded to the median of the values

Table 1. Summary of the patient characteristics and respective association with the risk of de novo HCC

Patient characteristics	Overall (*N* = 337)	Non-HCC (*N* = 324)	HCC (*N* = 13)	*p* value
Age at inclusion (mean±SD), years	59.7±10.9	59.6±11.0	59.9±11.9	$p = 0.43^3$
Sex, *n* (%)				$p = 0.53^4$
Male/female	243 (72.1)/94 (27.9)	232 (71.6)/92 (28.4)	11 (84.6)/2 (15.4)	
Ethnicity, *n* (%)				$p = 0.47^4$
Caucasian	274 (81.3)	263 (81.2)	11 (84.6)	
African	13 (3.9)	13 (4.0)	0 (0)	
Asian	3 (0.9)	2 (0.6)	1 (7.7)	
Unknown/nondisclosed	47 (13.9)	46 (14.2)	1 (7.7)	
Country of origin, *n* (%)				$p = 0.53^4$
Portugal	321 (95.3)	308 (95.1)	13 (100)	
Other country	8 (2.4)	8 (2.5)	0 (0)	
Unknown/nondisclosed	8 (2.4)	8 (2.5)	0 (0)	
Center of origin, *n* (%)				$p = 0.78^4$
ULSSM	92 (27.3)	89 (27.5)	3 (23.1)	
ULSTMAD	90 (26.7)	88 (27.2)	2 (15.4)	
ULSAS	53 (15.7)	50 (15.4)	3 (23.1)	
ULSSJ	41 (12.2)	40 (12.3)	1 (7.7)	
ULSLOD	27 (8.0)	25 (7.7)	2 (15.4)	
ULSLO	26 (7.7)	25 (7.7)	1 (7.7)	
ULSA	6 (1.8)	5 (1.5)	1 (7.7)	
ULSRL	2 (0.6)	2 (0.6)	0 (0)	
Marital status, *n* (%)				$p = 0.13^4$
Married	96 (28.5)	94 (29.0)	2 (15.4)	
Single	82 (24.3)	80 (24.7)	2 (15.4)	
Divorced	26 (7.7)	22 (6.8)	4 (30.8)	
Widowed	17 (5.0)	17 (5.2)	0 (0)	
Unknown/nondisclosed	116 (34.4)	111 (34.3)	5 (38.5)	
Age at diagnosis (mean±SD), years	45.2±13.2	45.2±13.2	46.0±15.2	$\mathbf{p < 0.001^3}$
Duration of disease until SVR (mean±SD), years	14.7±8.5	14.9±8.5	14.6±8.6	$p = 0.21^3$
Cirrhosis at diagnosis, *n* (%)	115 (34.1)	103 (31.8)	12 (92.3)	$\mathbf{p < 0.001^4}$
Compensated	99 (29.4)	90 (27.8)	9 (69.2)	
Decompensated	16 (4.7)	13 (4.0)	3 (23.1)	
HCV genotype, *n* (%)				$p = 0.50^4$
1	191 (56.7)	186 (57.4)	5 (38.5)	
2	7 (2.1)	7 (2.2)	1 (7.7)	
3	84 (24.9)	79 (24.4)	5 (38.5)	
4	37 (11)	36 (11.1)	1 (7.7)	
Unknown	18 (5.3)	17 (5.2)	1 (7.7)	
Alcohol use per day, in alcohol units (mean±SD)	4.8±3.5	4.8±2.3	4.7±3.2	$\mathbf{p = 0.03^3}$
Below the threshold[1], *n* (%)	69 (20.5)	69 (21.3)	0 (0)	
Above the threshold[1] (present/past), *n* (%)	93 (27.6)/46 (13.6)	86 (26.5)/44 (13.6)	7 (53.8)/2 (15.4)	
Never, *n* (%)	39 (11.6)	37 (11.4)	2 (15.4)	
Unknown/nondisclosed, *n* (%)	90 (26.7)	88 (27.2)	2 (15.4)	
Cigarette smoking, in pack-years (mean±SD)	33.3±40.0	33.3±40.1	33.5±39.3	$p = 0.82^3$
Active smoker/former smoker, *n* (%)	120 (35.6)/37 (11.0)	115 (35.5)/35 (10.8)	5 (38.5)/2 (15.4)	
Never, *n* (%)	49 (14.5)	48 (14.8)	1 (7.7)	
Unknown/nondisclosed, *n* (%)	131 (38.9)	126 (38.9)	5 (38.5)	

Table 1 (continued)

Patient characteristics	Overall (*N* = 337)	Non-HCC (*N* = 324)	HCC (*N* = 13)	*p* value
Drug use, *n* (%)				
Former user (injection drugs)/current user (injection drugs)	168 (49.9)/8 (2.4)	163 (50.3)/8 (2.5)	5 (38.5)/0 (0)	$p = 0.54^4$
Former user (any drug)/current user (any drug)	186 (55.2)/18 (5.3)	181 (55.9)/18 (5.6)	5 (38.5)/0 (0)	
Never	116 (39.9)	110 (34.0)	6 (46.2)	
Unknown/nondisclosed	32 (9.5)	30 (9.3)	2 (15.4)	
Blood transfusions[2], *n* (%)	9 (2.7)	7	2 (15.4)	$p = 0.63^4$
Hemodialysis, *n* (%)	6 (1.8)	6	0 (0)	$p = 0.79^4$
Tattoos and/or piercings, *n* (%)	31 (9.2)	31	0 (0)	$p = 0.36^4$
Comorbidities, *n* (%)				$\mathbf{p < 0.001^4}$
No	176 (52.2)	175 (54.0)	1 (7.7)	
Yes, other liver disease	41 (12.2)	36 (11.1)	5 (38.5)	
Yes, non-liver disease	102 (30.3)	96 (29.6)	6 (46.2)	
Unknown	18 (5.3)	17 (5.2)	1 (7.7)	
Hepatitis B, *n* (%)	6 (1.8)	6 (1.9)	0 (0)	$p = 0.79^4$
ALD, *n* (%)	33 (9.8)	29 (9.0)	4 (30.8)	$\mathbf{p = 0.03^4}$
MASLD, *n* (%)	12 (3.6)	11 (3.4)	1 (7.7)	$p = 0.85^4$
HIV, *n* (%)	3 (0.9)	3 (0.9)	0 (0)	$p = 0.89^4$
AHT, *n* (%)	33 (9.8)	32 (9.9)	1 (7.7)	$p = 0.64^4$
T2D, *n* (%)	27 (8.0)	27 (8.3)	0 (0)	$p = 0.61^4$
Dyslipidemia, *n* (%)	23 (6.8)	23 (7.1)	0 (0)	$p = 0.44^4$
BMI, kg/m^2 (mean±SD)	23.9±3.8	23.9±3.7	23.7±3.7	$p = 0.51^4$
BMI ≥25 kg/m^2/≥30 kg/m^2 (mean±SD)	37 (11.0)/25 (7.4)	35 (10.8)/24 (7.4)	2 (15.4)/1 (7.7)	$p = 0.61^4$/ $p = 0.57^4$
Ischemic heart disease, *n* (%)	7 (2.1)	7 (2.2)	0 (0)	$p = 0.86^4$
CKD, *n* (%)	10 (3.0)	10 (3.1)	0 (0)	$p = 0.73^4$
COPD, *n* (%)	9 (2.7)	9 (2.8)	0 (0)	$p = 0.79^4$
Non-HCC malignancy, *n* (%)	15 (4.5)	14 (4.3)	1 (7.7)	$p = 0.42^4$
Psychiatric disease, *n* (%)	23 (6.8)	23 (7.1)	0 (0)	$p = 0.40^4$
Antiviral treatment, *n* (%)				$p = 0.21^4$
One regimen	223 (66.2)	213 (65.7)	10 (76.9)	
Two or more regimens	61 (18.1)	58 (17.9)	3 (23.1)	
Unknown	53 (15.7)	53 (16.4)	0 (0)	
SVR after DAAs/SVR after interferon	282 (83.7)/2 (0.6)	269 (83.0)/2 (0.6)	13 (100)/0 (0)	
Stage of disease after SVR, *n* (%)				$\mathbf{p < 0.001^4}$
F0–1	136 (40.4)	135 (41.7)	1 (7.7)	
F2	53 (15.7)	53 (16.4)	0 (0)	
F3	57 (16.9)	57 (17.6)	0 (0)	
F4	91 (27.0)	79 (24.4)	12 (92.3)	

Table 1 (continued)

Patient characteristics	Overall (*N* = 337)	Non-HCC (*N* = 324)	HCC (*N* = 13)	*p* value
Child-Pugh after SVR, if cirrhosis (mean±SD)	5.4±1.0	5.4±1.0	5.4±1.1	**$p = 0.04$[4]**
A, *n* (%)	79 (86.8)	69 (21.3)	10 (76.9)	
B/C, *n* (%)	12 (13.2)	10 (3.1)	2 (15.4)	
MELD after SVR, if cirrhosis (mean±SD)	8.4±2.4	8.3±2.4	8.5±2.4	$p = 0.09$[4]

AHT, arterial hypertension; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LR, likelihood ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-stage Liver Disease; SD, standard deviation; SVR, sustained virologic response; T2D, type 2 diabetes mellitus; ULS(A), Unidade Local de Saúde (da Arrábida); ULSAS, ULS de Almada-Seixal; ULSLO, ULS Lisboa Ocidental; ULSLOD, ULS de Loures-Odivelas; ULSRL, ULS da Região de Leiria; ULSSJ, ULS São José; ULSTMAD, ULS Trás-os-Montes e Alto Douro. [1]>30 g/day and >20 g/day for males and females, respectively. [2]Before 1992. [3]Mann-Whitney U test. [4]χ^2 test/Fisher's exact test.

attained, with a minimum of 10 valid measurements and an interquartile range/median value <30%. The four stages of fibrosis defined according to LSM were F0–1 for values <7 kPa, F2 7–10 kPa, F3 >10 kPa, and F4 >13 kPa [19].

FIB-4 and aMAP were calculated post-SVR with the most recent laboratory data available after SVR. AFP was also assessed in the post-treatment context (first value available). The primary outcome of the study was de novo HCC and the secondary outcome was death by liver disease.

FIB-4 was calculated as follows: [age × AST]/[platelet count × $ALT^{1/2}$] [17]. The cutoff points for low- and high-risk groups were values of <3.25 and ≥3.25, respectively [9].

aMAP was calculated by applying the formula: ({0.06 × age + 0.89 × sex + 0.48 × [($\log_{10}$bilirubin × 0.66) + (albumin × −0.085)] − 0.01 × platelet count} + 7.4)/14.77 × 100 [9]. The cutoff points for the low-, moderate- and high-risk groups for HCC were <50, 50–60, and >60, respectively [3, 20].

Alcohol consumption above the threshold for metabolic dysfunction-associated steatotic liver disease was defined as >30 g/day and >20 g/day for males and females, respectively. Statistical analysis was performed using IBM SPSS Statistics 25. Measures of central tendency and dispersion were calculated for continuous variables, while categorical variables were reported with frequency tables. Group comparisons of categorical variables were performed using Pearson's χ^2 test (or Fisher's exact test if expected count <5). Mann-Whitney test was used for comparative analysis of continuous variables and the development of HCC. A multiple logistic regression analysis was performed. The areas under the curve (AUC) and respective receiver-operating characteristic analyses were calculated for TE, FIB-4, aMAP, and AFP to assess their predictive accuracy. Youden's J-statistic was used to obtain the optimized cutoffs regarding HCC development. A p value ≤0.05 was considered statistically significant.

Results

The present study included 337 patients from eight Portuguese centers. Table 1 displays the sociodemographic and clinical characteristics of the study population. Patients presented a mean age at inclusion of 59.7 years and most were male (72.1%), Portuguese (95.3%), and Caucasian (81.3%). The average duration of disease until SVR was 14.7 years. About one-third of patients had cirrhosis at diagnosis.

HCV genotype 1 was the most prevalent (also shown in Table 1). More than half of patients (*N* = 229, 68.0%) were treated with direct-acting antiviral agents (DAAs) as first therapy, while 55 (16.3%) were initially treated with interferon, with or without ribavirin. Overall, 83.7% achieved SVR after treatment with DAAs, while in the remaining patients it was either an unknown treatment (15.7%) or interferon (0.6%).

Table 1 summarizes the habits and comorbidities of the population. About half was a former/current smoker and a previous/current injection drug user. Excessive alcohol consumption was observed in 139 patients (41.2%). Alcohol-related liver disease (ALD) was the most common concomitant liver disease (9.8%). One or more cardiovascular risk factors were present in 72 patients (21.4%). The average body mass index was 23.9 kg/m^2, but it was unknown in 24.9% of patients. Regarding malignancies, 15 patients (4.5%) had one or more non-HCC cancer diagnosed during the follow-up. Three patients had cholangiocarcinoma (0.9%).

During a median follow-up of 31 months (interquartile range 20–57), 13 patients developed HCC (4.2%, 1.3/100 patient-years). On average, patients developed HCC 51.2 ± 28.4 months after the beginning of antiviral treatment. Only considering patients with advanced fibrosis according to the baseline LSM (*N* = 162, 48.1%), the incidence of HCC was 7.4% (3.2/100 patient-years). In this cohort of patients, the surveillance protocol was followed in 95.1% of cases (*N* = 154). Most cases were early-stage HCC (*n* = 6, 46.2%), seconded by stages B (*N* =

Table 2. Summary of the characteristics of the cohort of patients without advanced fibrosis at baseline

Patient characteristics	*N* = 175
Age at inclusion (mean±SD), years	57.5±10.4
Sex, *n* (%)	
Male/female	124 (70.9)/51 (29.1)
Ethnicity, *n* (%)	
Caucasian	142 (81.1)
African	7 (4.0)
Asian	2 (1.1)
Unknown/nondisclosed	24 (13.7)
HCV genotype, *n* (%)	
1	98 (56)
2	3 (1.7)
3	44 (25.1)
4	22 (12.6)
Unknown/nondisclosed	8 (4.6)
Comorbidities, *n* (%)	56 (32)
Alcohol use above the threshold[1] (present or past), *n* (%)	72 (41.1)
Smoker (active or former), *n* (%)	87 (49.7)
Hepatitis B, *n* (%)	2 (1.1)
ALD, *n* (%)	15 (8.6)
MASLD, *n* (%)	10 (5.7)
HIV, *n* (%)	1 (0.6)
AHT, *n* (%)	16 (9.1)
T2D, *n* (%)	10 (5.7)
Dyslipidemia, *n* (%)	12 (6.9)
BMI, kg/m^2 (mean±SD)	23.9±3.8
≥25 kg/m^2/≥30 kg/m^2	29 (16.6)/12 (6.9)
FIB-4 after SVR (mean±SD)	1.4±0.6
aMAP after SVR (mean±SD)	61.2±9.8
AFP after SVR, ng/mL (mean±SD)	4.8±1.6
HCC, *n* (%)	1 (0.6)

AHT, arterial hypertension; BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MASLD, metabolic dysfunction-associated steatotic liver disease; SD, standard deviation; SVR, sustained virologic response; T2D, type 2 diabetes mellitus. [1]>30 g/day and >20 g/day for males and females, respectively.

3, 23.1%) and C (*N* = 3, 23.1%), with only 1 case of stage D (7.7%).

On the other hand, in the cohort of patients F0–2 at baseline (*N* = 175, 51.9%), only 31.4% (*n* = 55) completed HCC surveillance per protocol. Almost one-third of patients (*N* = 56) in this cohort had other comorbidities, which are displayed in Table 2. One quarter (*N* = 44) was infected with HCV genotype 3.

Almost one-third of patients (*N* = 104, 30.9%) maintained surveillance until the end of the study. Follow-up was concluded in 169 patients (50.1%) due to hospital discharge, while in the remaining cases follow-up was lost (*N* = 43, 12.8%), or the patient died (*N* = 17, 5%) or was transferred (*N* = 4, 1.2%). Cause of death was liver-related in 47.1% of cases (*N* = 8), but only 5 patients died due to HCC (29.4%). In the remaining patients, the most common causes of death were infection (*N* = 4, 23.5%) or cardiovascular disease (*N* = 3, 17.6%).

Most patients were F0–1 (37.7%) or F4 (35.6%) at baseline according to LSM. At the subsequent measurements, after SVR, this distribution persisted (shown in Table 3). Almost all patients who developed HCC were F4 at baseline (92.3%), except one who was F0–1 (7.7%), both at baseline and after SVR (first measurement). Although all included patients had a baseline LSM, post-SVR TE was available in only 148 patients (43.9%), with only 45 patients (13.4%) with two LSM after SVR. The mean times between the beginning of antiviral treatment and the first and last LSM post-SVR were 14.9 ± 6.1 and 28.6 ± 23.2 months, respectively.

Table 4 shows the mean values of FIB-4, aMAP and AFP after SVR, and of LSM with TE at three different timepoints, when available. FIB-4 and aMAP were calculated in all patients and AFP was available in almost half of patients (*N* = 158, 46.9%).

Tables 1 and 4 display the comparative analysis of the different variables regarding the development of HCC, with age at inclusion and at diagnosis, cirrhosis at diagnosis, comorbidities, alcohol use and ALD, stage of disease after SVR, Child-Pugh after SVR, LSM at baseline, first measurement after SVR and last measurement after SVR, and FIB-4 after SVR exhibiting a statistically significant association with HCC. In the multivariate analysis, only age at diagnosis (OR 1.14; 95% CI: 1.00–1.29, $p = 0.01$) and median values of LSM before SVR (20.0 vs. 8.5 kPa; OR 1.05, 95% CI: 1.01–1.09, $p < 0.001$) remained as independent predictors.

Regarding the prediction of HCC in patients with at least a 24-month follow-up (*N* = 191, 56.7%), only LSM was significantly higher, both when measured before SVR ($p = 0.01$) and for the most recent measurement after SVR ($p = 0.04$), but none of the noninvasive tests studied presented statistical significance in the prediction of liver-related death (shown in Table 5).

Table 3. Absolute and relative frequencies of the fibrosis stage according to LSM by transient elastography divided by the three moments of measurement in the study

Liver stiffness measurement with transient elastography (FibroScan)	F0-1	F2	F3	F4
Baseline (N = 337), n (%)	127 (37.7)	48 (14.2)	42 (12.5)	120 (35.6)
After SVR (first) (N = 148), n (%)	38 (25.7)	27 (18.2)	33 (22.3)	50 (33.8)
After SVR (last) (N = 45), n (%)	22 (46.8)	8 (17)	2 (4.3)	15 (31.9)

LSM, liver stiffness measurement; SVR, sustained virologic response.

Table 4. Summary of the results attained with the noninvasive tests (transient elastography, FIB-4, and aMAP) and AFP and respective association with de novo HCC, and AUC values for predicting HCC development and the respective Youden-optimized cutoff

Noninvasive tests	HCC (N = 13)	Non-HCC (N = 324)	p value	AUC (95% CI)	Youden-optimized cutoff
Baseline LSM, kPa (mean±SD)	24.7±17.5	13.1±10.8	<**0.001**[1]	**0.776** (0.668–0.884)[3]	13.7
LSM after SVR (first), kPa (mean±SD)	25.9±22.3	10.2±7.4	<**0.05**[1]	**0.787** (0.504–1.000)[2]	16.5
LSM after SVR (last), kPa (mean±SD)	36.8±29.6	10.8±8.8	<**0.05**[1]	**0.935** (0.827–1.000)[2]	15.8
FIB-4 after SVR (mean±SD)	1.9±1.3	1.8±1.2	<**0.05**[1]	0.669 (0.527–0.812)[2]	1.6
aMAP after SVR (mean±SD)	62.2±9.6	62.3±9.5	=0.14[1]	0.622 (0.476–0.768)	58
AFP after SVR, ng/mL (mean±SD)	4.8±5.3	4.7±5.1	=0.07[1]	0.664 (0.490–0.839)[2]	4.4

AFP, alpha-fetoprotein; aMAP, age-male-ALBI-platelets; AUC, area under the curve; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; SD, standard deviation; SVR, sustained virologic response. [1]Mann-Whitney U test. [2]$p < 0.05$; [3]$p < 0.001$.

The cohort with a minimum follow-up of 24 months was stratified according to the aMAP score (presented in Table 6). The low-risk group was the less represented (9.9%), followed by the intermediate- and high-risk groups with 29.3% and 60.7%, respectively. Regarding fibrosis stage, 52.6% patients with scores <50 were F0–2 (N = 10), while 59.9% of patients with scores ≥50 were F3–4 (N = 103). There were no cases of HCC in the low-risk group (p = 0.62). Patients with a low-risk aMAP had an HCC incidence of 0% until the end of follow-up, while the intermediate- and high-risk groups had a 4-year, 6-year, and 8-year cumulative HCC incidence of 1.8%/2.1%, 1.8%/6.3%, and 7.1%/8.3%, respectively. The cutoff of 50 resulted in a sensitivity and a negative predictive value (NPV) of 100%, while the cutoff of 60 resulted in a specificity of 94.7% and a positive predictive value of 9.4%.

The predictive accuracy of TE, FIB-4, aMAP, and AFP regarding the development of HCC is presented in Table 4. FIB-4, aMAP, and AFP showed a weak accuracy. Regarding TE, the values measured before SVR (AUC 0.776) and the first LSM after SVR (AUC 0.787) revealed a fair accuracy to identify HCC. The most recent LSM presented the numerically highest AUC (0.935).

The following cutoffs that denote a high versus low risk for HCC were identified: baseline LSM >13.7 kPa (sensitivity 85% and specificity 69%), LSM after SVR (first) >16.5 kPa (sensitivity 75% and specificity 88%), LSM after SVR (last) >15.8 kPa (sensitivity 100% and specificity 87%), FIB-4 >1.6 (sensitivity 85% and specificity 53%), aMAP >58 (sensitivity 92% and specificity 29%), and AFP >4.4 (sensitivity 73% and specificity 66%) (shown in Table 4). Regarding patients who were F3–4 according to baseline LSM (n = 162), almost one-third had a baseline LSM ≤13.7 kPa (n = 51, 31.5%), an FIB-4 ≤1.6 (n = 50, 30.9%), and an aMAP ≤58 (n = 48, 29.6%), with an NPV of 98%, 94%, and 96%, respectively, when considering the development of HCC.

Table 5. Comparison of the predictive accuracy of transient elastography, FIB-4, and aMAP regarding the development of HCC and liver-related death after a minimum follow-up of 24 months

Noninvasive tests	Outcome	*N*	*p* value[1]
Baseline LSM, kPa	HCC	191	**0.01**
	No	178	
	Yes	13	
	Liver-related death	191	0.09
	No	180	
	Yes	11	
LSM after SVR (first)	HCC	96	0.08
	No	92	
	Yes	4	
	Liver-related death	96	0.57
	No	93	
	Yes	3	
LSM after SVR (last)	HCC	45	**0.04**
	No	43	
	Yes	2	
	Liver-related death	45	0.34
	No	43	
	Yes	2	
FIB-4 after SVR	HCC	191	0.34
	No	178	
	Yes	13	
	Liver-related death	191	0.07
	No	180	
	Yes	11	
aMAP after SVR	HCC	191	0.15
	No	178	
	Yes	13	
	Liver-related death	191	0.27
	No	180	
	Yes	11	

aMAP, age-male-ALBI-platelets; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; SVR, sustained virologic response. [1]Mann-Whitney U test.

Discussion

Early detection of HCC is a key component toward potentially reducing HCC mortality [1, 2, 8, 9, 12, 21]. In the study by Chhatwal et al. [2], HCC surveillance was cost-effective above an HCC incidence rate of 0.7/100 patient-years, a threshold that could allow an earlier diagnosis of HCC. Personalized surveillance strategies are urgently needed to optimize resource allocation since the number of HCC surveillance candidates post-SVR will

Table 6. Number of patients according to aMAP group, fibrosis stage, and HCC in the cohort with a minimum 24-month follow-up

aMAP risk group	F0–2[1] (*N* = 79)		F3–4[1] (*N* = 112)		All patients (*N* = 191)	
	HCC (*N* = 1)	Non-HCC (*N* = 78)	HCC (*N* = 12)	Non-HCC (*N* = 100)	HCC (*N* = 13)	Non-HCC (*N* = 178)
Low (<50), *n* (%)	0 (0)	10 (13)	0 (0)	9 (9)	0 (0)	19 (11)
Medium (50–60), *n* (%)	0 (0)	26 (33)	4 (33)	26 (26)	4 (31)	52 (29)
High (>60), *n* (%)	1 (100)	42 (54)	8 (67)	65 (65)	9 (69)	107 (60)

aMAP, age-male-ALBI-platelets; HCC, hepatocellular carcinoma. [1]According to baseline liver stiffness measurement.

increase more than sixfold until 2030 [1, 2]. Also, the exact stage of disease is unconfirmed by liver biopsy, and the diagnosis of cirrhosis in clinical practice is subject to substantial variations [3, 12, 13, 22]. In our study, the incidence of HCC was 1.3/100 patient-years and almost half of patients had advanced liver disease, features that are consonant with published data [1, 5, 20].

Considerable evidence supports the use of LSM for predicting HCC risk in HCV [14, 16, 22, 23]. However, specific cutoffs for identifying at risk patients vary substantially, ranging from ≥19 to 30 kPa pretreatment and ≥10–20 kPa posttreatment [1, 12, 16]. The thresholds used in untreated patients have proven inaccurate after SVR, and the lower cutoffs need further validation [12, 13, 22].

In this study, TE proved to be a fair predictor of HCC when measured before SVR (AUC 0.776, $p < 0.001$) and the authors recognized the potential utility of LSM, both before SVR and during follow-up of these patients [24, 25]. Almost all patients who eventually developed HCC were F4 at baseline, with a mean LSM of 24.7 kPa. Even though all LSMs at the three different timepoints were positively associated with the development of HCC, the most significant was baseline LSM ($p = 0.001$).

Even though TE was a fair to excellent predictor of HCC when used in the post-SVR context, these results should be cautiously interpreted since less than half of patients had an LSM after SVR. Especially regarding the last LSM after SVR, this was only available in 45 patients with two incident cases of HCC. Accordingly, the authors consider that for prediction purpose, only the baseline and first measurement post-SVR should be considered.

LSM of <13.7 kPa at baseline presented an acceptable sensitivity (85%) and could be used to categorize the post-SVR HCV patients as of low risk for HCC, with a yearly reassessment in order to exclude an increase of liver stiffness over the years. However, the authors have to highlight the rare but noteworthy exceptions where patients without advanced fibrosis also develop HCC after SVR. Also, LSMs are sometimes impossible to obtain in obese patients, and reproducibility is reduced in steatosis, higher body mass index, and lower levels of liver fibrosis [6].

FIB-4 is considered a weak predictor of HCC according to some studies regarding HCC risk after SVR [1]. On the contrary, Li et al. stated that the performance of FIB-4 was superior to all the other scores evaluated [6]. In our study, the discriminative power of FIB-4 to predict HCC was weak. The Youden-optimized cutoff identified for the prediction of HCC was 1.6, which presented an acceptable sensitivity.

Only 69% of the patients who developed HCC had an aMAP score deemed of high risk (>60). However, aMAP performed exceptionally well for predicting the absence of HCC for scores <50. Additionally, the cutoff of 58 presented an NPV of 96% regarding the development of HCC in the cohort of patients with advanced fibrosis. Thus, there is a potential role for aMAP in excluding patients from surveillance, since one-third of patients in this cohort had a score ≤58. Still, the majority of patients scored in the groups of intermediate risk or high risk, implying that all of these would still need HCC surveillance, probably in a more aggressive manner, which could lead to a decrease of the cost-effectiveness [18]. These findings deeply contrast with the results published by Fan et al. [3] in which the group of aMAP <50 accounted for almost half of the population. Interestingly, approximately half of the patients with an aMAP <50 in our study did not have advanced fibrosis, so surveillance would not have been recommended in any case according to current guidelines. On the contrary, almost half of patients with an aMAP ≥50 would have been excluded from HCC surveillance since they were at a fibrosis stage ≤F2.

In our study, aMAP score showed a weak accuracy to predict HCC and it did not associate with statistical significance with HCC. Accordingly, this score did not adequately stratify the HCC risk after SVR between the

intermediate- and high-risk groups, especially at the 8-year timepoint when the cumulative HCC incidence was 7.1% and 8.3%, respectively. This discrepancy might be due to the fact that more than 33% of the population included in this study had cirrhosis, whereas aMAP performs less well in this cohort of patients, which are underrepresented in the validation cohorts [18, 20]. Also, a higher number of patients and a greater adherence to surveillance would certainly empower the discriminative power to predict HCC, recently validated by Johnson et al. [20]. However, the cutoff of 60 resulted in an acceptable positive predictive value (9.4%). This score could have performed better if the design was prospective, but the authors consider that further validation in the Portuguese population will be necessary. aMAP score is already considered the best HCC prediction model, and this promising tool can revolutionize HCC risk stratification [20].

The sensitivity of AFP alone for HCC screening when using a threshold of 20 ng/mL varies from 41% to 65% [8, 11]. Moreover, AFP has showed high AUC for HCC prediction in several studies and was included in a risk prediction model at a cutoff of ≥4.6 ng/mL, a considerably lower value than the cutoffs generally proposed [1]. Our study corroborated the cumulative evidence that AFP values are significantly lower in the context of HCC prediction, with a mean value of 4.8 ng/mL in the patients who developed HCC and an optimal cutoff of 4.4 ng/mL. However, the accuracy of this laboratory test was weak.

In this study, the F0–1 patient who eventually developed HCC was infected with HCV genotype 3 and diagnosis was made 90 months after the start of antiviral treatment. In terms of other risk factors for HCC, the patient was older, smoked, and drank >30 g/day of alcohol. HCC screening was implemented by the assistant physician in this particular case, wherein aMAP score was high risk (67), while FIB-4 and AFP were low risk (2.7 and 1.6 ng/mL, respectively).

Our study corroborates that both alcohol use and ALD should be clearly distinguished as risk factors for HCC in this context [1, 26]. Also, older age, advanced fibrosis/cirrhosis, LSM with TE, and FIB-4 were relevant risk factors for HCC. Even though ALD and AHT were the most common comorbidities, metabolic dysfunction-associated steatotic liver disease was probably underestimated. Nonetheless, the authors did not observe a significant association between metabolic comorbidities and HCC after SVR, which corroborates recent studies [1].

This study portrays some relevant data regarding the epidemiological and clinical characterization of the post-SVR HCV population in Portugal, which has been growing in the last years. HCV genotype 1 was the most prevalent, which follows the Western European epidemiology [5, 27]. The average duration of disease until SVR was considerably long. However, with the general availability of the DAAs, it is expected that patients reach SVR earlier, with a possible impact in the incidence of HCC.

In our study, all HCV patients with SVR were included, independently of the estimated degree of fibrosis. However, surveillance is sometimes performed in this group in a case-by-case basis, especially in the presence of risk factors for HCC. Even though surveillance was only uptaken in about one-third of F0–2 patients, this allowed the finding of a case of HCC in this cohort. This relevant bias could be surpassed in future prospective studies. Also, since HCC cases that developed in the first year after antiviral therapy were excluded, the calculated incidence of HCC in our study must be regarded reckoning this shortcoming, and the proposed cutoffs may only be considered after this time frame. Furthermore, the retrospective design introduced considerable variability regarding the timepoint for the assessment of posttreatment data. Nonetheless, this heterogeneity may actually improve the strength of the risk stratification approach since some variation is inevitable in clinical practice.

Another limitation is the fact that the median follow-up was relatively short, which was surpassed by only considering the patients with at least a 24-month follow-up in the statistical analysis regarding incident HCC. Additionally, as recently demonstrated by Toyoda et al. [4], there are marked variations in the characteristics and prognosis of post-SVR HCC across regions. Since the vast majority of included patients were Portuguese and Caucasian, it remains to be shown whether our findings can be extrapolated to other populations.

Regarding the staging of HCC at diagnosis, the authors highlight that even though almost all patients with advanced fibrosis fulfilled HCC surveillance, the rate of early HCC was considerably low (46.2%). In fact, early diagnosis of HCC is not common in the West, but this is frequently associated with the low uptake of surveillance programs [20]. Consequently, our results further strengthen the rationale that liver ultrasound for screening of HCC is not suitable or sensitive enough for the detection of early HCC [8, 9, 11]. Also, the quality of the liver ultrasounds performed in our study was not controlled, which could also possibly explain a lower rate of early HCC.

As a strength, the authors highlight that few studies have specifically addressed the performance of noninvasive

tests in the post-SVR context, which is a topic that needs further studies and validation of the different cutoffs found in order to potentially exclude patients from the burdensome surveillance program. An optimal prediction model for this specific subgroup is highly anticipated since both LSM and noninvasive scores present dynamical changes post-SVR, which might impair the performance of current models [18, 20].

Conclusion

Transient elastography (FibroScan) before SVR was a fair predictor of HCC (AUC 0.776, $p < 0.001$), proving more accurate than FIB-4 and aMAP. LSM values ≤13.7 kPa at baseline stratify a Portuguese cohort of cured HCV patients with advanced fibrosis as of low risk for HCC. aMAP and FIB-4 proved useful for identifying almost one-third of patients with advanced fibrosis as low risk, with optimal cutoffs of 58 and 1.6, respectively.

The current screening strategy missed 7.7% of the HCC cases in this study, which could have been surpassed by the aMAP score, but not transient elastography or FIB-4. aMAP score is a promising and simple tool for HCC risk assessment, but needs further validation in the Portuguese population.

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Statement of Ethics

Written informed consent was obtained from participants (or their next of kin) to participate in the study. This study protocol was reviewed and approved by Comissão de Ética para a Saúde do Centro Hospitalar de Lisboa Ocidental on November 22, 2021 with the Approval No. 2199.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

André Mascarenhas, Rita Barosa, and Pedro Figueiredo were responsible for the conception of the study protocol. André Mascarenhas, Ana Rita Franco, Pedro Lima, Catarina O'Neill, Raquel R. Mendes, and Inês Rodrigues Simão reviewed the state of the art. André Mascarenhas, André Ruge Gonçalves, Rui Mendo, Rita Barosa, and Pedro Figueiredo performed the statistical analysis and interpretation of the acquired data. All coauthors contributed to acquisition of data, revision, and final approval of the work.

Data Availability Statement

All data generated or analyzed during this study are included in the article. Further inquiries can be directed to the corresponding author.

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