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REVIEW

Predicting Hepatocellular Carcinoma Risk in Patients with Chronic HCV Infection and a Sustained Virological Response to Direct-Acting Antivirals

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Abstract: Chronic infection with hepatitis C virus (HCV) may complicate with hepatocellular carcinoma (HCC), especially in patients with cirrhosis. Although the achievement of a sustained virological response (SVR) had been associated with a reduction in the risk of HCC already in the Interferon era, some concerns initially raised following the use of direct-acting antivirals (DAA), as their use was associated with increased risk of HCC development and aggressiveness. However, studies demonstrated that the risk of HCC was strongly influenced by pre-treatment fibrosis stage and, eventually, prior HCC history more than the type of antiviral therapy. According to published studies, rates of de-novo HCC ranged between 1.4% and 13.6% in patients with cirrhosis or advanced fibrosis vs 0.9% and 5.9% in those with chronic hepatitis C (CHC). Conversely, rates of recurrent HCC were higher, ranging between 3.2% and 49% in cirrhotics vs 0% and 40% in CHC patients. Most studies tried to identify predictors of HCC development, either de-novo or recurrent, and some authors were also able to build predictive scores for HCC risk stratification, which however still need prospective validation. Whereas some clinical features, such as age, gender, presence of comorbidities and fibrosis stage, may influence both de-novo and recurrent HCC, previous tumour burden before DAA seems to prevail over these features in recurrent HCC risk prediction.

Keywords: hepatocellular carcinoma, HCC, hepatitis C virus, HCV, sustained virological response, SVR, direct-antiviral agent, DAA, surveillance, predictor

Introduction

Hepatocellular carcinoma (HCC) is currently the fourth cause of liver-related death worldwide,[1,2] and accounts for one of the most frequent indications for liver transplantation. In patients with chronic hepatitis C (CHC), the achievement of a sustained virological response (SVR) to antiviral treatment was demonstrated to reduce the incidence of HCC, already in the Interferon (IFN) era,[3–6] with a more pronounced benefit in those with advanced fibrosis or cirrhosis. After direct-acting antivirals (DAA) approval, a first pivotal study suggested a time-related association between DAA treatment and HCC recurrence,[7] this finding being initially supported by others.[8,9] Similarly, some authors also reported an increased incidence and biological aggressiveness of de-novo HCC arising in cirrhotics successfully treated with DAA.[9–11] Next, evidences eventually raised against a definite role of oral anti-hepatitis C virus (HCV) treatments as HCC promoter.[12–19] Different crude incidences of HCC in IFN vs DAA-treated cirrhotics mostly rely on differences in

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patient population, as DAA allow treatment of patients with more advanced liver diseases. Following an SVR to DAA-based regimens, reported rates of de-novo HCC are estimated nearly 2–2.5%[17,20–22] vs 20–30% per year[18,19,23] of recurrent HCC, being definitively higher than that historically reported in the setting of IFN.[4] Moreover, HCC risk has been demonstrated to persist up to 10 years from treatment completion.[17]

Taking together, these data still justify the need for long-life surveillance,[1,24] resulting in intensive follow-up of large cohorts of cured HCV patients. Therefore, current literature efforts aim at deeply investigating predictors of HCC in HCV patients cured through SVR, with the ultimate goal of personalized risk stratification and individualized surveillance policies.

Therefore, in this review, we report data from published study analyzing the risk of HCC development, either de-novo or recurrent, following DAA-based treatments. Particularly, we focused on those studies reporting not only full patients' characteristics but also information on HCC rates and predictors.

Predictors of de-novo HCC

According to published studies, up to 14% of patients without history of previous liver cancer may develop de-novo HCC after HCV eradication, although data vary according to patient population, follow-up duration and severity of liver disease (Table 1).

Studies Enrolling Patients with Cirrhosis or Advanced Fibrosis

Among 14 studies that reported data in cirrhotic patients,[8,10,20–22,25–37] (Table 2), most were able to identify HCC predictors (Table 3). In addition, 5 studies enrolling patients with CHC and any fibrosis stage also found-out factors associated with de-novo HCC in the subset of patients with cirrhosis[38–42] although unable to provide their clinical features (Tables 4 and 5). Finally, 5 authors reported data on patients with advanced fibrosis, defined through histology (F3-F4), non-invasive tests or criteria for chronic advanced liver disease (cACLD)[11,36,43–46] (Table 2). Eight out of these studies enrolled only patients with an SVR,[10,21,30,33,37,44–46] whilst in one study data could be extrapolated.[34] In studies including also non-SVR patients, rates of treatment failure ranged between 1.9% and 10% (Table 2). Follow-up duration varied according to study designs as reported in Table 2. Overall, studies reported de-novo HCC rates of 1.8–13.6% in cirrhotics, and of 1.4–4.6% in patients with advanced fibrosis.

Table 1 Assessment of Liver Fibrosis Severity According to Studies' Designs

Liver Disease Severity	Tool for Staging	Authors
Cirrhosis		
Histology	METAVIR F4	Conti,[8] Cabibbo,[13] Calvaruso,[20] Degasperi,[22] Nahon,[21] Pol,[23] Ravaioli,[25] Degasperi,[26] Rinaldi,[27] Lleo,[28] Degapseri,[31] Finkelmeier,[35] Pinero,[39] Tanaka,[42] Alonso Lopez,[45] Tamaki[48]*, Nagata,[54] Kogiso[65]
Clinical	Any clinical features US features	Cabibbo,[13] Calvaruso,[20] Degasperi,[22] Ravaioli,[25] Rinaldi,[27] lleo,[28] Degasperi,[26] Degasperi,[31] Sangiovanni,[32] Ogawa,[38] Alonso Lopez,[45] Kwon,[51] Ogawa,[55] Kogiso,[65] Zou[67]
FIB-4	>3.25 Not specified	Tanaka,[42] Nagata[54] Ide[40]
LSM	≥12 kPa >12 kPa >12.5 kPa ≥12.5 kPa ≥ 13.5 kPa ≥14.9 kPa >16.2 kPa Not specified	Conti,[8] Bergna,[30] Sangiovanni,[32] Ogasawara[57] Cabibbo,[13] Calvaruso,[20] Casadei-Gardini[29] Ravaioli,[25] Lleo,[28] Finkelmeier,[35] Virlogeux[61] Pinero,[39] Tanaka,[42] Seholm[53] Rinaldi[27] Ogawa[38] Bergna,[30] Shiha[44] Rinaldi,[36] Ogawa[55]
ICD codes		Kanwal,[34] Kanwal,[41] Zou[67]
Advanced fibrosis		
Histology	METAVIR F3-F4	Nagata[54]
LSM	>9.5 kPa >10 kPa ≥10 kPa >10.2 and ≤16.2 kPa	Pinero,[39] Alonso Lopez[45] Ogawa[38] Pons,[46] Seholm[53] Shiha[44]
FIB-4	>3.25	Tani,[52] Nagata,[54] Watanabe[59]
APRI	≥1	Watanabe[59]

Notes: *Available in 191 out of 346 patients.
Abbreviations: F, fibrosis; US, ultrasound; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; APRI, AST to platelet ratio; ICD, international classification of diseases (code).

Table 2 Characteristics of Studies Reporting Data on HCC Occurrence (de-novo HCC) in Patients with Cirrhosis or Advanced Fibrosis

Author	Enrollment Period	Study Design	Patients	Males	Age	Fibrosis	CPT Score	SVR	HCC	Follow-Up
Cirrhosis (n=18)										
Conti, 2016[8]	Italy 2015	Multicenter, retrospective	285	167 (59%)	61 (37–86)	LSM 24.4 ± 0.88	CPT-A 256 CPT-B 29	261 (91.6%)	9 (3.1%) SVR 7 CPT-A 5	24 w°°
Cardoso, 2016[10]	Portugal 2015	Single-center, retrospective	54	38 (70%)	41–81	APRI 1.02–4.04	CPT-A 34	54 (100%)	4 (7.4%) CPT-A 67%	12.0 (IQR 9.4–12.5) m°°°°°
Kanwal, 2017[34]	US 2015	Multicenter, retrospective	7495#	NA	NA	NA	NA**	7495 (100%)	139 (1.8%)	NA
Ravaioli, 2018[25]	Italy 2015–2016	Single-center, retrospective	119	91 (65.5%)§	63 (52–73)§	LSM§ 18.6 (15.0–26.0) FIB-4§ 4.7 (3.0–6.8) APRI§ 1.67 (0.86–2.63)	CPT-A 108 CPT-B 11	131 (94.2%)ç	13 (10.8%)	15 (12–19) m°° ç
Calvaruso, 2018[20]	Italy 2015–2016	Multicenter, prospective	2249	1280 (57%)	65 ± 11	LSM 22.4 ± 11.9	CPT-A 2035 CPT-B 214	2140 (95.2%)	78 (3.4%) SVR 64	14 (6–24) m
Nahon, 2018[21]	France 2014–2016	Multicenter, prospective	336	212 (63%)	59 (54–67)	NA	CPT-A 173 CPT-B 19 CPT-C 1***	336 (100%)	15 (4.5%)	21.2 (IQR 13.5–26.9) m°
Finkelmeier, 2018[35]	Germany 2014–2016	Single-center, retrospective	269	183 (68%)	58 (29–86)	LSM 20.6 (6.1–63.9)	CPT-A 211 CPT-B 50 CPT-C 8	242 (90%)	25 (3.6%) CPT-A 24 CPT-B 1	364 (0–950) d°
Degasperi, 2019[22]	Italy 2014–2016	Single-center, longitudinal	505	302 (60%)	63 (28–87)	LSM 19.1 (12.0–75.0)	CPT-A 442 CPT-B 63	546 (97%)ç	28 (4.9%)	25 (3–39) m°
Degasperi, 2019[26]	Italy 2014–2016	Single-center, retrospective	452	58%	63 (28–87)	LSM 19.1 (12.0–75.0) FIB-4 4.9 (0.3–46.0)	CPT-A 393 CPT-B 59	96%	31 (6.9%)	33 (3–47) m°

(*Continued*)

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Table 2 (Continued).

Author	Enrollment Period	Study Design	Patients	Males	Age	Fibrosis	CPT Score	SVR	HCC	Follow-Up
Rinaldi, 2019[27]	Italy 2015–2017	Multicenter, prospective	258	143 (55%)	68 (61–74)	LSM 25.5 (18.0–35.6)	CPT-A 242 CPT-B 16	NA	35 (13.6%) CPT-A 30	NA
Rinaldi, 2019[36]	Italy 2015–2017	Multicenter, prospective	731	NA	NA	NA	CPT-A 649 CPT-B 82	714 (97.7%)	35 (4.8%) SVR 33 25 CPT-A	48 w°°
Lleo, 2019[28]	Italy 2015	Multicenter, longitudinal	1766	1094 (62%)	1529 (87%) ≥50	500 (28%) LSM ≥25	CPT-A 1561 CPT-B 201	1679 (95.1%)	50 (2.8%) SVR 9 CPT-A 37	NA
Casadei-Gardini, 2019[29]	Italy 2015–2016	Multicenter, retrospective	416	242 (58%)	63 (31–90)	NA	CPT-A 351 CPT-B 65	NA	29 (7%)	18 (0.4–26.4) m°ç
Abe, 2020[37]	Japan	Multicenter, retrospective	188	90 (48%)	70 (61–77)	FIB-4 6.2 (4.3–8.7)	CPT-A 188*	188 (100%)	19 (10%)	46 (37–52) m°°
Degasperi, 2020[31]	Italy 2014–2016	Single-center, retrospective	452	261 (58%)	63 (28–87)	LSM 17.4 (12.0–75.0) FIB-4 4.9 (0.3–46.3)	CPT-A 393 CPT-B 59	96%ç	36 (7.9%) CPT-A 31	43 (3–57) m°
Sangiovanni, 2020[32]	Italy 2015–2017	Multicenter, prospective	1161	686 (59%)	65 (22–85)	NA	CPT A 1066	1119 (96%)	48 (4.1%) SVR 47	17 (3–43) m°
Fan, 2020[33]	East Asia, Europe, US 2014–2016	Prospective, observational cohorts or RCT	2489	71%	55 (46–63%)	NA	2.489 (100%)**	2489 (100%)	NA	NA
Bergna, 2021[30]	Italy	Single-center, retrospective	577	58%	64	LSM 17.3	CPT-A 513 CPT-B 64	577 (100%)	46 (8%)	52 (8–62) m°
Advanced Fibrosis (n=5)										
Romano, 2018[11]	Italy 2015–2017	Multicenter, prospective	3917 F3/F4	2437 (62%)	58 (21–90)	LSM 18.8 (1.1–75.0) FIB-4 4.7 (3.0–6.8) APRI 1.8 (0.1–43.1)	2958**** (CPT-A 2388) (CPT-B 352)	2637 (94%)	55 (1.4%) SVR 33 F4 55 CPT-A 38	536 ± 198 d°

Rinaldi, 2019[36]	Italy 2015–2017	Multicenter, prospective	985 F3/F4	543 (55%)	67 (59–73)	LSM 17.3 (11.9–35.3)	731 (CPT-A 649) (CPT-B 82)	966 (98.1%)	35 (3.6%) SVR 33 F4 35 CPT-A 25	48 w°°
Shiha, 2020[44]	Egypt 2015–2018	Multicenter, observational	2372 F3/F4	1242 (52%)	56 (50–62)	NA	1734 (CPT-A 1294) (CPT-B 440)	2372 (100%)	109 (4.6%) F4 101 CPT-A 66	23.6 ± 8.3 m°°
Alonso Lopez, 2020[45]	Spain 2015–2017	Multicenter, observational	993 F3/F4	551 (55.5%)	62 (26–88)	LSM 19.0 ± 10.7 FIB-4 4.1 ± 3.8	NA*	993 (100%)	35 (3.9%)	17 (3–43) m°
Pons, 2020[46]	Spain 2015–2016	Multicenter, prospective	572 cACLD	282 (49.3%)	64 ± 11	LSM 20.2 ± 10.4 FIB-4 5.6 ± 4.4	NA*	572 (100%)	25 (4.4%)	2.9 (0.3–3.8) y

Notes: Values are expressed as median (range), mean ± standard deviation and/or percentages (%). Age is calculated in years-old; LSM is calculated in kPa. °From DAA start; °°From EOT; °°°From SVR12; °°°°From SVR24; °°°°°From HCV-RNA undetectability. #Patients with and without an SVR were included in the study. cAvailable for patients with and without HCC history. *Only CPT-A patients included; **CPT criteria at enrollment not available; ***CPT score available in 193; ***CPT score available in 2640. LSM by FibroScan®.

Abbreviations: HCC, hepatocellular carcinoma; CPT, Child-Pugh-Turcotte score; SVR, sustained virological response; F, fibrosis; LSM, liver stiffness measurement; IQR, interquartile range; w, weeks; NA, not available; FIB-4, fibrosis-4 index; APRI, AST to platelet ratio index; m, months; y, years; F4, cirrhosis; US, United States; cACLD, chronic advanced liver disease; DAA, direct-acting antivirals; EOT, end of treatment; RCT, randomized controlled trials.

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Table 3 Incidence and Risk Factors of de-novo HCC in Patients with Cirrhosis or Advanced Fibrosis

Author	SVR Status	Incidence of HCC (CumI)								Independent Predictors
		CumI							100 PY	
		6-Month	1-Year	1.5-Year	2-Year	3-Year	4-Year	5-Year		
Cirrhosis (n=16)										
Conti, 2016[8]	SVR + non-SVR	3.1%	–	–	–	–	–	–	–	NA
Cardoso, 2016[10]	SVR	–	–	–	–	–	–	–	–	None
Kanwal, 2017[34]	SVR	–	–	–	–	–	–	–	1.82	Race (Hispanic)
Ravaioli, 2018[25]	SVR + non-SVR	–	–	–	–	–	–	–	–	ΔLSM <30%, CPT-B
Calvaruso, 2018[20]	SVR + non-SVR°	–	**SVR** 2.9%° CPT-A SVR 2.1% CPT-B SVR 7.8%	–	–	–	–	–	–	Albumin, PLT, non-SVR
Nahon, 2018[21]	SVR + non-SVR	–	–	–	–	5.9%	–	–	SVR 1.4 Non-SVR 14	Age >50 years, past alcohol, HCV-1, PLT <150/mm^3, γGT ≥2 ULN
Finkelmeier, 2018[35]	SVR + non-SVR	–	–	–	–	–	–	–	–	Non-SVR
Degasperi, 2019[22]	SVR + non SVR	1,4%	3.4%	4.7%	5.7%	6.0%	–	–	–	**Model 1:** Male gender, LSM, DM **Model 2:** Male gender, FIB-4, DM
Degasperi, 2019[26]	SVR + non-SVR	–	–	–	–	7.5%	–	–	–	Male gender, FIB-4, DM
Rinaldi, 2019[27]	SVR + non-SVR	–	–	–	–	–	–	–	–	Age, LSM, PLT
Rinaldi, 2019[36]	SVR + non-SVR	–	4.7%	–	–	–	–	–	–	Male gender, DM, SOF-based + RBV-free therapy, CPT-B
Lleo, 2019[28]	SVR + non-SVR	0.9%	2.4%	3.5%	–	–	–	–	–	Age (≥50 years), non-SVR, EV

Casadei-Gardini, 2019[29]	NA	0.010°°	0.05°°	0.072°°	–	–	–	–	–	ALBI, PLT
Abe, 2020[37]	SVR	–	2.6%	–	4.9%	9.3%	11.5%	–	–	**Model 1:** ALBI (2,3) **Model 2:** ALBI (2,3), DM, PLT
Degasperi, 2020[31]	SVR + non-SVR	–	–	–	–	–	9%	–	–	Male gender, albumin, DM, GRS >0.597
Sangiovanni, 2020[32]	SVR + non-SVR	–	–	–	–	7.8%	–	–	3.1	αFP, ascites, UNMN
Advanced fibrosis (n=5)										
Romano, 2018[11]	SVR + non-SVR	–	F3 0.46% F4 1.18% CPT-A 1.49% CPT-B 3.61%	–	F3 0% F4 NA CPT-A 0.20% CPT-B 0.69%	–	–	–	0.97	**F4:** APRI >2.5, HBV co-infection
Rinaldi, 2019[36]	SVR + non-SVR	–	3.6%	–	–	–	–	–	–	Male gender, LSM, DM, SOF-based + RBV-free therapy
Shiha, 2020[44]	SVR	–	–	–	–	–	–	–	2.3	Age, male gender, αFP, albumin, cirrhosis
Alonso Lopez, 2020[45]	SVR	–	1.4%	–	2.2%	4.1%	–	–	–	LSM, albumin, ΔLSM (1-year), ΔFIB-4 (1-year)
Pons, 2020[46]	SVR	–	–	–	–	–	–	–	1.5	**Pre-DAA:** albumin **SVR48:** albumin + LSM <10 kPa

Notes: °CumI are available for SVR patients, only (vs predictors of HCC); °°cumulative Hazards of HCC occurrence. LSM by FibroScan®.

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virological response; CumI, cumulative incidence; PY, person/year; F4, cirrhosis; NA, not available; LSM, liver stiffness measurement; CPT, Child-Pugh-Turcotte score; PLT, platelets; HCV, hepatitis C virus; γGT, γ-glutamyl-transferase; DM, diabetes mellitus; FIB-4, Fibrosis-4 index; SOF, sofosbuvir; RBV, ribavirin; EV, esophageal varices; CSPH, clinically significant portal hypertension; ALBI, albumin-bilirubin score; MELD, model for end-stage liver disease; αFP, alpha-fetoprotein; GRS, genetic risk score; UNMN, undefined/non-malignant nodule; HBV, hepatitis B virus; DAA, direct-acting antivirals.

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Table 4 Characteristics of Studies Reporting Data on HCC Occurrence (de-novo HCC) in Patients with Chronic Hepatitis C (Any Fibrosis Stage)

Author	Enrollment Period	Study Design	Patients	Males	Age	Fibrosis	Cirrhosis (F4)	SVR	HCC (Number)	Follow-Up
Any Fibrosis Stage (n=23)										
Kanwal, 2017[34]	US 2015	Multicenter, retrospective	19,518[#]	18,851 (97%)	62 ± 6	NA	7495 (38%)**	19,518 (100%)	183 (0.9%)	20,415 PY
Tachi, 2017[56]	Japan 2014–2015	Multicenter, prospective	233	108 (46%)	16–88	ARFI 0.67–4.35	NA**	233 (100%)	7 (3.0%)	18.1 (5.6–31.2) m[°ç]
Nagata, 2017[54]	Japan 2014–2017	Multicenter, retrospective	669	340 (45%)[ç]	69 (24–87)[ç]	FIB-4 3.0 (0.2–74.7)[ç]	F3-F4** 108 (33%)[ç]	722 (96%)[ç]	7 (1.1%)	1.8 (0.1–7.7) y[°ç]
Ogawa, 2018[38]	Japan 2015–2016	Multicenter	1523	660 (43%)	66 (54–73)	NA	271 (18%)*	1523 (100%)	20 (1.3%)	17 (1–23) m[°]
Finkelmeier, 2018[35]	Germany 2014–2016	Single-center, retrospective	819	470 (57%)	55 (18–86)	LSM 5.6 ± 9.4	269 (33%) (CPT-A 211) (CPT-B 50) (CPT-C 8)	764 (93.3%)	25 (3%) SVR 20 F4 25 CPT-A 24	263 (0–1001) d[°]
Degasperi, 2019[26]	Italy 2014–2016	Single-center, retrospective	348	48%	60 (21–88)	LSM 8.1 (2.0–11.9)	0	NA	3 (0.9%)	23 (5–42)
Rinaldi, 2019[36]	Italy 2015–2017	Multicenter, prospective	966	529 (55%)	67 (59–73)	LSM 16.0 (22.8–23.0)	731 (76%)	966 (100%)	35 (3.6%)	48 w[°°]
Watanabe, 2019[50]	Japan 2014–2017	Multicenter, retrospective	1174[#]	540 (46%)	65.3 (23–88)	NA	NA**	1174 (100%)	33 (2.8%)	539 d[°°]
Hiraoka, 2019[60]	Japan 2014–2017	Multicenter, retrospective	1069 (484 DC, 585 VC)	478 (48%)	67 ± 11	FIB-4 2.76±1.77	NA**	1069 (100%)	36 (3.4%) 14 DC, 22 VC	16.3 ± 9.5 m[°°°]
Tamaki, 2019[48]	Japan 2015–2017	Single-center	346	126 (36%)	68 ± 10	NA	21 (6%)**	346 (100%)	24 (6.9%)	26.4 ± 7.9 m[°°°]
Higuchi, 2019[58]	Japan 2015–2017	Single-center	304	109 (36%)	68 ± 11	145 (48%) FIB-4 >3.245	NA**	304 (100%)	18 (5.9%)	21.1 ± 6.5 m[°°°]
Iio, 2019[47]	Japan 2014–2018	Multicenter, retrospective	1029	435 (42%)	NA (20–90)	NA	NA*	1029 (100%)	19 (1.8%)	104 w[°°]
Pinero, 2019[39]	S. America 2016–2018	Multicenter, prospective	1400	668 (48%)	58 ± 12	NA	784 (56%)** CSPH 399	1114/1149 (96.9%)	30 (2.3%) F4 28	16 (IQR 8.9–23.4) m[°]
Ide, 2019[40]	Japan 2015–2017	Multicenter, prospective	2552	1003 (4.0%)	65 (20–92)	FIB-4 3.86 ± 3.22	648 (25%)**	2552 (100%)	70 (2.7%) F4 35	22.6 ± 8.3 m[°]

Kwon, 2019[51]	Korea 2015–2017	Multicenter retrospective	562	264 (45%)[c]	59 ± 12[c]	NA	172 (29%)**[c]	461/487 (97%)[c]	15 (2.6%) SVR 15 F4 10	1 y[°°,c]
Ogasawara, 2020[57]	Japan 2010–2017	Single-center, retrospective	398	154 (38%)	70 (25–88)	LSM 8.6 (2.4–49.6) FIB-4 3.00 (0.63–19.15)	NA*	398 (100%)*	19 (4.8%)	3.3 (0.5–7.1) y[°°°]
Tani, 2020[52]	Japan 2014–2018	Multicenter	1088	545 (50%)	68 (58–75)	FIB-4 2.94 (1.85–4.63) APRI (0.86–1.55)	191 (18%)**	1088 (100%)	26 (2.4%) F4 10	13.8 m[°°]
Kanwal, 2020[41]	US 2015	Multicenter, retrospective	18,076	17,446 (96.5%)	62 ± 6	5614 (28.8%)	6938 (38.4%) **	18,076 (100%)	544 (3.0%)	2.93 ± 0.56 y[°°]
Abe, 2020[37]	Japan	Multicenter, retrospective	880 (F0-F3)	421 (48%)	66 (56–74)	FIB-4 2.4 (1.6–3.6)	0	880 (100%)	20 (2.2%)	42 (31–48) m[°°]
Tanaka, 2020[42]	East Asia 2014–2018	Multicenter, retrospective	5646[#]	2404 (43%)	64 ± 12	3.81 ± 3.24	2911 (52%) (CPT-A 1314) (CPT-B/C 79)	5646 (100%)	244 (4.3%) F4 221	2.93 y[°°°]
Ogawa 2020[55]	Japan 2014–2019	Multicenter, retrospective	2405	1057 (43.9%)	43–81	1.02–5.74	501 (21%)*	2405 (100%)	64 (2.7%)	3.5 (1–5.2) y[°]
Watanabe 2020[59]	Japan 2014–2017	Multicenter, retrospective	1438	663 (46%)	66 ± 10	NA	NA**	1401 (97%)	55 (3.8%)	803 days[°°]
Seholm, 2020[53]	Denmark 2012–2019	Multicenter, retrospective	773 CHC	492 (64%)	54 (45–61)	LSM 11.6 (2.5–75.0)	F3-F4 45 (58%)	773 (100%)	11 (1.4%) F3-F4 10	36 (6–82) m[°°°°]

Notes: Values are expressed as median (range), mean ± standard deviation and/or percentages (%). Age is calculated in years-old; LSM is calculated in kPa. [°]From DAA start; [°°]From EOT; [°°°]From SVR12; [°°°°]From SVR24; [°°°°°]From pLSM. [#]Patients with and without an SVR were included in the study. [c]Available for patients with and without HCC history. *Only CPT-A patients included; **CPT criteria at enrollment not available. LSM by FibroScan®.

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virological response; US, United States; PY, person-years; F4, cirrhosis; F, fibrosis; LSM, liver stiffness measurement; ARFI, acoustic radiation force impulse; DC, derivation cohort; VD, validation cohort; CPT, Child-Pugh-Turcotte score; w, weeks; m, months; y, years; NA, not available; FIB-4, fibrosis-4 index; APRI, AST to platelet ratio index; CSPH, clinically significant portal hypertension; IQR, interquartile range; DAA, direct-acting antivirals; EOT, end of treatment; pLSM, pre-treatment LSM.

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Table 5 Incidence of de-novo HCC and Factors Associated with HCC Occurrence (de-novo HCC) in Patients with Chronic Hepatitis C (Any Fibrosis Stage) from 21 Studies

Author	SVR Status	Incidence of HCC (CumI)								Independent Predictors
		CumI							100 PY	
		6-Month	1-Year	1.5-Year	2-Year	3-Year	4-Year	5-Year		
Kanwal, 2017[34]	SVR	–	–	–	–	–	–	–	0.90	**F0-F3:** FIB-4 ≥3.25, DM, alcohol **Overall:** cirrhosis, alcohol, race
Tachi, 2017[56]	SVR	–	2.3%	–	4.3%	–	–	–	–	LSM by ARFI
Nagata, 2017[54]	SVR + non-SVR	–	–	–	–	1.4%	–	–	–	IL28B, SVR24 WFA*M2BP
Ogawa, 2018[38]	SVR	–	**F0-F3** 0.4% **F4** 4.9%	–	–	–	–	–	–	**Overall:** EOT-αFP, cirrhosis **F0-F3:** PLT, advanced fibrosis **F4:** EOT-αFP, portal hypertension
Degasperi, 2019[26]	SVR + non-SVR	–	–	–	–	2%	–	–	–	**NA**
Watanabe, 2019[50]	SVR	–	1.9%	3.2%	4.1%	–	–	–	–	**Pre-DAA:** male gender, albumin, FIB-4 **EOT:** FIB-4, αFP
Hiraoka, 2019[60]	SVR	–	–	–	–	–	–	–	–	Male gender, SVR12-FIB-4 >3.25, SVR12-αFP >5 ng/mL
Tamaki, 2019[48]	SVR	–	–	–	–	–	–	–	–	Age, SVR12-αFP ≥6.5 ng/mL, SVR12-LSM by MRE ≥3.75 kPa, LR3/4 nodules
Higuchi, 2019[58]	SVR	–	–	–	–	–	–	–	–	Age, SVR12-LSM by MRE ≥3.75, SVR-12 αFP ≥6 ng/mL
Iio, 2019[47]	SVR	–	–	–	–	–	–	–	–	αFP >4.6 ng/mL, FIB-4 >2.67, TLL1 AT/TT
Pinero, 2019[39]	SVR + non-SVR	–	**Overall** 0.02% **F4** 0.003%		**Overall** 0.04% **F4** 0.06%	–	–	–	–	**Overall:** CSPH, non-SVR, previous IFN **F4:** CSPH, non-SVR

Ide, 2019[40]		–	**Overall** 1.3% **F0-F3** 0.9% **F4** 2.5%	–	**Overall** 2.9% **F0-F3** 2.1% **F4** 5.2%	**Overall** 4.9% **F0-F3** 2.9% **F4** 10.0%	–	–	–	**Overall:** Male gender, age>62, FIB-4, γGT **F0-F3:** Male gender, age, γGT **F4:** Male gender, FIB-4 ≥4.6
Kwon, 2019[61]	SVR + non-SVR	–	–	–	–	–	–	–	–	EOT-αFP
Ogasawara, 2020[57]	SVR	–	0.8%	–	3.0%	–	6.0%	–	–	LSM ≥20 kPa, αFP ≥8 ng/mL, SVR24-LSM ≥10 kPa
Tani, 2020[52]	SVR	0.61%	1.88%	2.82%	3.71%	6%	–	–	–	Age>75, post-EOT αFP
Kanwal, 2020[41]	SVR	–	**Overall** 1.1% **F4** 2.2%	– **F4** 3.8%	**Overall** 1.9% **F4** 5.6%	**Overall** 2.8% **F4:** Age, race (non-African American, MELD)	–	–	–	**Overall:** Age, race (non-African American), alcohol, HCV-3
Abe, 2020[37]		–	0.7%	–	1.1%	1.8%	3.0%	–	–	**F0-F3:** albumin
Tanaka, 2020[42]	SVR	–	–	–	–	–	–	**F0-F3** 1.35% **F4** 14.9%		**F0-F3:** αFP ≥10 ng/mL **F4:** Age ≥60, αFP ≥10 ng/m, ALBI 2–3
Ogawa, 2020[55]		–	–	–	–	–	–	–	0.56–3.61	**Pre-DAA:** Age (60–84), male gender, cirrhosis **SVR12:** albumin, ALT, αFP, ΔFIB-4
Watanabe, 2020[59]		–	**Overall** 2.3% **Females** 1.3% **Males** 3.2%	–	**Overall** 3.9% **Females** 2.8% **Males** 5.2%	**Overall** 4.9% **Females** 3.4% **Males** 6.7%	**Overall** 14.4% **Females** 8.8% **Males** 19.2%	–	–	**Females:** FIB-4, EOT-αFP **Males:** EOT-αFP
Seholm, 2020[53]	SVR	–	–	–	–	–	–	–	0.5	Age, LSM ≥17.5 kPa

Notes: Values are expressed as median (range), mean ± standard deviation and/or percentages (%). LSM by FibroScan®.

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virological response; CumI, cumulative incidence; PY, person/year; F, fibrosis; F4, cirrhosis; FIB-4, fibrosis-4 index; DM, diabetes mellitus; LSM, liver stiffness measurement; ARFI, acoustic radiation force impulse; DAA, direct-acting antivirals; WFA*M2BP, *Wisteria floribunda* agglutinin positive Mac-2 binding protein; EOT, end of treatment; αFP, alpha-fetoprotein; MRE, magnetic resonance elastography; TLL1, tolloid-like 1 gene; IFN, interferon; CSPH, clinically significant portal hypertension; γGT, γ-glutamyl-transferase; HCV, hepatitis C virus; ALT, alanine aminotransferase.

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Table 6 Cumulative Incidence (Cuml) of HCC According to Values of Clinically Significant Variables

Author	Fibrosis	Clinical Variables	Cut-Off	1-Year	2-Year	3-Year	4-Year
de-novo HCC							
Ogawa, 2018[38]	F4	EOT-αFP	<9 vs ≥9 ng/mL	1.4% vs 13.1%	–	–	–
Degasperi, 2019[22]	F4	LSM by TE **(Model 1)**	≤30 vs >30 kPa	–	–	5% vs 20%	–
		FIB-4 **(Model 2)**	≤9 vs >9	–	–	5% vs 10%	–
Rinaldi, 2019[27]	F4	LSM by TE*	<20 vs 20–30 vs >30 kPa	–	–	–	–
Abe, 2020[37]	F4	ALBI	≤2.3 vs >2.3	1.6% vs 7.5%	2.4% vs 11.5%	4.2 vs 23.4%	5.2 vs 26.3%
	F4	PLT**	≥82 vs <8210^3/mm^3	–	–	–	–
	F4	DM**	No vs Yes	–	–	–	–
Degasperi, 2020[31]	F4	Gender	Female vs Male	–			6% vs 12%
	F4	DM	No vs Yes	–	–	–	7% vs 17%
	F4	Albumin	≥3.5 vs <3.5	–	–	–	7% vs 21%
	F4	GRS	≤0.597 vs >0.597	–	–	–	7% vs 16%
Pons, 2020[46]	cACLD	SVR48-LSM ***	<10 vs.10–20 vs ≥20 kPa	–	–	–	–
	cACLD	Albumin***	<4 vs ≥ 4 g/dl	–	–	–	–
Tachi, 2017[56]	CHC	LSM by ARFI	<1.73 vs ≥1.73	1.2 vs 6.1%	1.2 vs 13.4%	–	–
Tamaki, 2019[48]	CHC	SVR12-LSM by MRE	<3.75 vs ≥3.75 kPa	1.4% vs 6.6%	2.5% vs 11.9%	2.5% vs 14.5%	–
Iguchi, 2019[58]	CHC	SVR12-LSM by MRE	<3.75 vs ≥3.75 kPa	0.5% vs 6.7%	1.7% vs 11.9%	–	–
Watanabe, 2019[50]	CHC	FIB-4 < vs ≥4****	<4 vs ≥4	–	–	–	–
	CHC	Albumin****	<3.8 vs ≥3.8 g/dl	–	–	–	–
	CHC	Gender****	Female vs Male	–	–	–	–
	CHC	αFP****	<6 vs ≥6 ng/mL	–	–	–	–
Iio, 2019[47]	CHC	TLL1	AA vs AT/TT	1.3% vs 3.6%	1.5% vs 5.5%	–	–
Seholm, 2020[53]	CHC	LSM by TE*****	<17.5 vs ≥17.5 kPa	–	–	–	–
Watanabe, 2020[59]	CHC	Gender	Female vs Male	1.3% vs 3.2%	2.8% vs 5.2%	3.4% vs 6.7%	8.8% vs 19.2%
	CHC	αFP (females)*****	<6 vs ≥6 ng/mL	–	–	–	–
		αFP (males)*****	<3.5 vs ≥3.5 ng/mL	–	–	–	–
Abe, 2020[37]	F0-F3	Albumin******	≥3.95 vs <3.95 g/dl	–	–	–	–
	F0-F3	αFP******	<6 vs ≥6 ng/mL	–	–	–	–

Recurrent HCC									
Degasperi, 2020[31]	F4	DM Ethnicity	No vs Yes Italian vs Egyptian	– –	–	– –	– –	–	45% vs 88% 48% vs 100%
Ikeda, 2017[62]	CHC	Number of HCC treatments	1 vs 2–3 vs ≥4	18.1% vs 28.2% vs 60.2%	–	22.1% vs 41.6% vs 74.5%	–	–	–
Nakano, 2019[66]	CHC CHC	Number of HCC treatments αFP	<3 vs ≥3 <5.4 vs ≥5.4 ng/mL	30.7% vs 43.8% 18.9 vs 30.0%	–	45.6% vs 67.1% 31.6% vs 48.1%	56.4% vs 68.6% 45.5% vs 53.2%	–	–
Zou, 2019[67]	CHC CHC CHC	Palliative treatments Time tx HCC-DAA SVR	No vs Yes >4 vs 2–4 vs 1–2 years Yes vs No	0% vs 5.1% 0 vs 2.3% vs 5.0% 0 vs 3.6%	–	4.4% vs 29.5% 3.9% vs 16.0% vs 28.6% 17.9% vs 44%	–	–	–

Notes: Only CumI with significant statistical differences (p-value) have been reported. *p=0.019; **PLT ≥82 vs <82$10^3$/mm3: p<0.05; DM no vs yes: p<0.05; ***SVR48-LSM <10 vs. 10–20 vs ≥20 kPa: 0.7 vs 1.7 vs 3.2 PY; albumin ≥ vs <4 g/dl: 1.0 vs 2.3 PY; ****FIB-4 < vs ≥4: p<0.001; Albumin > vs ≥3.8 g/dl: p<0.001; Female vs Male: p=0.018; αFP < vs ≥6 ng/mL: p<0.002; *****p=0.017; ******Females < vs ≥6 ng/mL: p=0.023; Males < vs ≥3.5 ng/mL: p=0.041 at 1500 day; *******Albumin ≥ vs <3.95 g/dl: p=0.0013; αFP < vs ≥6 ng/mL: p=0.0035; DM No vs Yes: p<0.0007; FIB-4 < vs ≥3.25: p=0.0008 [No correspondent CumI available in all studies].

Abbreviations: HCC, hepatocellular carcinoma; CHC, chronic hepatitis C; F4, cirrhosis; LSM, liver stiffness measurement; ARFI, acoustic radiation force impulse; EOT, end of treatment; αFP, alpha-fetoprotein; SVR12, sustained virological response; MRE, elasto-MR; TLLI, tolloid-like receptor; TE, transient elastography; FIB-4, fibrosis-4 index; ALBI, albumin-bilirubin score; PLT, platelets; DM, diabetes mellitus; GRS, genetic risk score; NA, not available.

Cumulative incidences (CumI) for each study are reported in Table 3.

Severity of Liver Disease

In the setting of cirrhosis, severity of liver disease was identified among the most important predictors of de-novo HCC, and was assessed either through non-invasive tests for fibrosis staging or clinically.

Liver Stiffness Measurement (LSM)

Several studies reported an association between de-novo HCC and LSM, mainly assessed by transient elastography (TE). LSM was correlated with HCC occurrence either when analysed at a single time-point [mostly pre-DAA (baseline)], or as a dynamic variable, by evaluating changes in LSM values between pre- and post-treatment. Thresholds able to discriminate patients at different risk of HCC development varied according to studies (Table 6). For example, Degasperi et al found that the 3-year probability of HCC significantly increased in cirrhotics with baseline LSM values >30 kPa, while Rinaldi et al used the 20 kPa and 30 kPa thresholds[22,27] (Table 6). In addition, Ravaioli et al reported an increased risk of de-novo HCC in patients with a <30% decrease in LSM values, between baseline and the end of treatment (EOT).[25]

In F3-F4 patients, one European study reported that high baseline TE values as well as changes in LSM (ΔLSM) one-year after EOT were associated with an increased risk of de-novo HCC. Pre-treatment LSM >17.3 kPa and ΔLSM >25.5% were finally included in a predictive model (see below)[45] (Table 7). These results were not confirmed by Pons et al, reporting that the risk of de-novo HCC in cACLD patients was independent of LSM improvement, either when using the 30% or 20% decline cut-offs. Conversely, the risk of de-novo HCC was increased by LSM values >10 kPa one-year after EOT.[46]

Serological Non-Invasive Tests (NITs)

Among NITs, Fibrosis-4 Index (FIB-4) was the most used to assess fibrosis severity. Baseline FIB-4 emerged as an independent risk factor for de-novo HCC in some studies analysing cirrhotic patients,[22,26,40] although different cut-offs were identified (Table 6). Degasperi et al reported a significantly higher 3-year de-novo HCC incidence in patients with baseline FIB-4 >9, while Ide et al identified the alternative 4.6 cut-off, that was therefore incorporated in a composite predictive score (see below)[40] (Table 7). In F3-F4 patients, Alonso Lopez et al found that both

Table 7 Studies Reporting Predictive Scores for de-novo HCC

Study	Fibrosis	Score Name	Variables Included	Algorithm	Risk Classes	HCC Rate According to Risk Classes
Abe, 2020[37]	F4	NA	ALBI score° PLT° DM status	0 or 1 points ALBI score ≤ or >2-3 PLT ≥ or < 8.2 x 10^4/μL Absence or presence of DM	0–1 Low-score 2–3 High-score	Low vs High-score Group 0.7% vs 12.5% at 1 yr 2.2% vs 15.2% at 2 yrs 3.1% vs 33.9% at 3 yrs 3.1% vs 41.2% at 4 yrs
Fan, 2020[33]	F4	aMAP	Age Gender Bilirubin Albumin PLT	Mathematical Formula	<50 Low-risk 50–60 Intermediate Risk >60 High-Risk	Low vs Intermediate vs High-Risk 0–0.8% vs 1.5–4.8% vs 8.1–17.8% at 3–5 yrs
Shiha, 2020[44]	F3-F4#	GES	Age° Male gender αFP° Albumin° Fibrosis	0 points to 3.5 points Female vs Male Age ≤ or > 54 years Albumin ≥ or <3.8 g/dl αFP ≤ or >20 ng/mL F3 or F4	GES ≤6 Low Risk GES 6–7.5 Intermediate Risk GES >7.5 High Risk	Low vs Intermediate vs High-Risk 0.1% vs 0.7% vs 1.2% at 1 yr 1.2% vs 3.3% vs 7.1% at 2 yrs 1.9% vs 5.8% vs 9.5% at 3 yrs
Alonso-Lopez, 2020[45]	F3-F4*	NA	**LSM Model** Albumin° LSM° SVR48 ΔLSM§ **FIB-4 Model** Albumin° FIB-4° SVR48 FIB-4§ SVR48 γGT§	**LSM Model (0 or 1 points)** Albumin ≥ or < 4.2 g/dl LSM ≤ or > 17.3 kPa ΔLSM ≥ or <25.5% **FIB-4 Model (0 to 2 points)** Albumin ≥ or <4.2 g/dl FIB-4 ≤ or >3.7 SVR48 FIB-4 ≤ or >3.3 SVR48 γGT ≤ or >42 U/l	**LSM Model** Score 0-1-2-3 **FIB-4 Model** Score 1–2 vs 3–4 vs 5–6	**LSM Model** Score 0 vs 1 vs 2 vs 3 0% vs 2.1% vs 5.8% vs 16.3% at 3 yrs **FIB-4 Model** Score 1–2 vs 3–4 vs 5–6 0.4% vs 1.7% vs 6.5 vs 19% at 3 yrs

Watanabe, 2019[50]	CHC	NA	**Pre-DAA Model** FIB-4° Albumin° Gender **Post-DAA Model** EOT FIB-4 EOT AFP	**Pre-DAA Model** 0 or 1 points FIB-4 < or ≥4.0 Albumin > or ≤3.8 g/dl Female or Male **Post-DAA Model** 0 or 1 points FIB-4 < or ≥4.0 AFP< or ≥6.0 ng/mL	**Pre-DAA Model** 0 Low Risk 1–2 Intermediate Risk 3 High Risk **Post-DAA Model** 0 Low 1 Intermediate 2 High	**Pre-DAA Model** Low vs Intermediate vs High Risk 0.4% vs 2.1% vs 9.5% at 1 yr 0.4% vs 4.4% vs 16.4% at 2 yrs **Post-DAA Model** Low vs Intermediate vs High Risk 0.4% vs 1.4% vs 6.1% at 1 yr 0.4% vs 3.2% vs 14.4% at 2 yrs
Hiraoka, 2019[60]	CHC	ADRES	Gender SVR24 FIB-4 SVR24 αFP	1 point to each variable Male FIB-4 >3.25 αFP >5 ng/mL	ADRES 0-1-2-3	ADRES 0 vs 1 vs 2 vs 3 0% vs 0.5% vs 8.4% vs 18% at 1 yr 0% vs 1.6% vs 13.4% vs 32.8% at 2 yrs
Iio, 2019[47]	CHC	NA	SVR24 AFP SVR24 FIB-4 TLL1 AA/TT	1 point to each variable αFP >4.6 ng/mL FIB-4 >2.67 TLL1 AA/TT	0 Low Risk 1–2 Intermediate Risk 3 High Risk	Low vs Intermediate vs High Risk 0% vs 2.2% vs 10.4% at 1 yr 0% vs 3.0% vs 13.6% at 2 yrs
Tani, 2020[52]	CHC	NA	EOT Age EOT αFP	0 to 1 points Age < or ≥75 years-old AFP < or ≥6 ng/mL	Score 0-1-2	Score 0 vs 1 vs 2 0.3% vs 1.05% vs 4.92% at 1 yr 0.3% vs 6.27% vs 18.37% at 2 yrs 1.26% vs 10.45% vs 18.37% at 3 yrs

Notes: °Pre-DAA; §1 year after EOT. *LSM>9.5 kPa; #LSM>10.2 kPa for F3; LSM >16.3 for F4.

Abbreviations: ALBI, Albumin to Bilirubin Index; αFP, Alpha-fetoprotein; CHC, Chronic Hepatitis C; DAA, Direct-acting antivirals; DM, Diabetes; EOT, End of Treatment; FIB-4, Fibrosis-4 index; γGT, gamma-glutamyl transferase; HCC, Hepatocellular carcinoma; LSM, Liver Stiffness Measurement; PLT, platelets; SVR, Sustained Virological Response; TLL1, Tolloid-like protein 1; yr, year; yrs, years; 24SVR, 24 weeks after EOT; SVR48, 48 weeks after EOT.

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baseline FIB-4 >3.7 and FIB-4 >3.3 one year after treatment were associated with de-novo HCC[45] (Table 7). Other NITs had been investigated as predictors of HCC in several studies: the albumin-bilirubin (ALBI) score grade 2–3[29,37,42] and AST to platelet (PLT) ratio index (APRI) >2.5[11] emerged as independent risk factors for de-novo HCC in patients with cirrhosis and advanced fibrosis, respectively.

Portal Hypertension and Surrogates of Advanced Liver Disease

The risk of de-novo HCC was also increased in cirrhotic patients with clinical features of more advanced liver disease, irrespective of LSM and/or NIT values. The presence of portal hypertension (PH) was an independent predictor of HCC in several studies, although definition of PH was heterogeneous. Ogawa et al defined PH by either LSM values (≥20 kPa) or hepatic venous pressure gradient (HVPG; >10 mmHg), or by imaging.[38] Thus, among indirect markers of PH were both biochemical tests and clinical features. For example, albumin[20,31,37,44,45] and PLT[20,21,27,29] were independently associated with HCC occurrence, either as single predictors or when included in predictive scores (Tables 6 and 7). The presence of esophageal varices (EV)[28] or ascites was associated with an increased the risk of de-novo HCC.[32]

Clinical scores incorporating these parameters, such as Child-Pugh-Turcotte (CPT)[25,36] and Model for End Stage Liver Disease (MELD)[41] or ALBI scores[29,37,42] were independently associated with de-novo HCC in cirrhotics (Table 7). Some studies provided different CumI of de-novo HCC according to the combination of one or more variables associated with portal hypertension (see below).

Patient-Related Factors

Several patients' features, either modifiable or not modifiable, have been shown to increase the risk of de-novo HCC after the achievement of an SVR. Age was independently associated with HCC occurrence in most studies[21,27,28,40–42,44] as well as male gender[22,26,31,36,40,44] (Tables 3 and 5). In US cohorts, a role of non-African American ethnicity has been suggested,[34,41] although this association deserves further confirmation. Among comorbidities, diabetes mellitus (DM) has been associated with an increased risk of HCC in several cohorts;[22,26,31,36,37] Abe et al incorporated DM status in a multivariable HCC risk score (see below) (Table 7). Other factors such as alcohol consumption,[21,41] and viral co-infections[11] are likely to influence post-SVR HCC risk, although these patients were systematically excluded from most clinical trials.

Genetic Predictors

A single-center study conducted in a large cohort of DAA-treated cirrhotic patients found that a genetic risk score combining 4 single nucleotide polymorphisms (SNPs) [PNPLA3, TM6SF2, MBOAT7 and GCKR] was an independent predictor of de-novo HCC, together with other clinical predictors (DM, male gender, albumin values)[31] (Tables 3 and 6). The same authors found that the tolloid-like 1 (TLL1) gene, which had been previously associated with HCC occurrence in Japanese CHC patients,[47] did not predict de-novo HCC in 348 European cirrhotics.[26]

Virus-Related Factors

Two studies, only, reported that HCV genotype might influence the risk of HCC during follow-up. Nahon et al found that HCV-1 patients were at increased risk of HCC development,[21] whilst genotype 3 was independently associated with de-novo HCC in a large retrospective study from US[41] (Table 3).

Alpha-Fetoprotein (αFP)

Although not universally recommended for HCC surveillance by international guidelines due to its low sensitivity and specificity, broad application of αFP in routine clinical practice has led many authors to investigate its potential for de-novo HCC prediction. αFP was independently associated with HCC occurrence, either in patients with cirrhosis[32,38,42] or advanced fibrosis.[44] Some studies evaluated the predictive ability of αFP assessed at baseline,[32,42,44] while others analysed the EOT time-point.[38] Most studies tried to identify a predictive αFP cut-off: overall, the proposed cut-offs resulted always higher than the reference standard 7 ng/mL (ie, >9 or ≥10 ng/mL, >20 mg/mL)[38,42,44] (Tables 3 and 6).

Undefined Nodules

Sangiovanni et al found that the presence of undefined/non-malignant nodules at baseline was an independent predictor of HCC occurrence in cirrhotic patients.[32] Partially in line with this finding is what reported by Tamaki et al, as they found that Li-Rads 3/4 nodules were independently associated with HCC occurrence in CHC patients (6.9% cirrhotics).[48] To avoid biases related to inclusion of patients carrying nodules at risk of HCC transformation, presence of undefined nodules was declared to be an exclusion criterion in some studies[10,22,26,31,36] (Table 3).

Lack of a Sustained Virological Response

Some studies including large cohorts of treated patients did not allow separate analysis of those achieving an SVR, thus leading to include non-SVR among potential predictors of de-novo HCC. Although the statistical power when analysing the influence of non-SVR status on HCC risk, some authors reported that the lack of an SVR was associated to increased HCC occurrence[20,28,34,35,39] (Table 3).

Combined Predictors and HCC Risk Scores

The risk of de-novo HCC increased when two or more independent predictors identified at multivariable analysis were combined. Not surprisingly, in all cases HCC cumulative incidences (CumI) proportionally increased according to the number of risk factors considered.[11,20,22,28,46] These studies mostly included parameters associated with liver disease severity (LSM, APRI, CPT score, PLT, albumin), DM and SVR status. Conversely, 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, gender, presence of DM) and biochemical variables (albumin, γGT, PLT, αFP) together with data related to liver disease severity.[33,37,44,45] The aMAP score failed in predicting de-novo HCC in 2085 F3-F4 patients with HCV-4,[49] and, similarly, GES score performance was suboptimal in a Caucasian cohort.[30] Cumulative incidences of de-novo HCC according to different risk classes are reported in Table 7.

Studies Enrolling Patients with Chronic Hepatitis C (Any Fibrosis Stage)

Twenty-three studies reported data on HCC occurrence in CHC patients with any stage of liver fibrosis (Table 3). Almost all these studies included cirrhotic patients; rates of cirrhotics ranged between 6% and 73%, although some authors did not provide this information. Most studies included only patients with an SVR, whilst data could be extrapolated from three studies.[34,42,50] In studies including non-SVR patients, treatment failure accounted for 3.0–6.7% of DAA treatment responses (Table 4).

Overall, 0.9% to 6.9% of CHC patients developed de-novo HCC during follow-up, although only few authors reported the prevalence of cirrhosis in CHC cohorts. When reported, rates of cirrhosis were between 38% and 100% in CHC patients developing HCC[35,39,40,51–53] (Table 4), and overall CumI of de-novo HCC were lower than that reported in cirrhotic cohorts, at each time-point (Tables 2 and 4).

Severity of Liver Disease

Due to the inclusion of cirrhotic patients in CHC cohorts, liver disease severity was independently associated with HCC occurrence in most studies. Only 5 studies were able to identify HCC predictors in non-cirrhotic F0-F3 patients,[34,37,38,40,42] and three of them included indirect markers of fibrosis, either biochemical tests or NITs (see below) (Table 5).

Cirrhosis and Advanced Fibrosis

Whatever defined, cirrhosis and advanced fibrosis were independently associated with HCC development in several studies.[34,38,39,54,55] In these studies, cirrhosis was differently defined (Table 1), and ranged between 18% and 56% of the overall population. Particularly, the CHC cohort described by Pinero et al included 399 (29%) patients with clinically significant portal hypertension (CSPH) (Table 4).

Liver Stiffness Measurement

Baseline LSM obtained by Acoustic Radiation Force Impulse (ARFI) or TE, was associated with an increased risk of post-treatment HCC (Table 5) in three studies analysing SVR patients.[53,56,57] Tachi et al identified the 1.73 m/s threshold as the optimal cut-off to stratify CHC patients according to their de-novo HCC risk[56] (Table 5). In the other two studies, baseline LSM ≥20 kPa and ≥17.5 kPa were associated with HCC occurrence in 398 and 773 CHC patients from Japan and Denmark, respectively. In both studies, the prevalence of cirrhosis was not reported.-[53,57] Ogasawara et al reported that also SVR24-LSM (ie, LSM performed 24 weeks after EOT) ≥10 kPa was independently associated with de-novo HCC.[57] This finding was in line with two other Japanese studies, identifying in LSM ≥3.75 kPa obtained through Magnetic Resonance Elastography (MRE) 12 weeks after treatment completion (SVR12-MRE) an independent predictor of HCC occurrence.[48,58]

Serological Non-Invasive Tests

Most studies reported that either baseline or post-treatment FIB-4 values were associated with the risk of de-novo HCC in CHC patients. In 5 studies, baseline FIB-4 was

reported to be an independent risk factor for HCC occurrence.[34,40,47,50,59] Risk thresholds varied according to each study: Kanwal et al used the standard 3.25 cut-off,[34] whereas Iio et al used the 2.67 cut-off.[47] In the study by Watanabe et al, baseline FIB-4 predicted HCC in females, only.[59] In addition, three Japanese studies reported that post-SVR FIB-4 (at EOT and at SVR12) and changes in FIB-4 independently predicted de-novo HCC.[50,55,60] Among investigated serological biomarkers of fibrosis was *Wisteria floribunda* agglutinin positive Mac-2 (WFA*M2BP), which was tested in the study by Nagata et al, reporting that WFA*M2BP assessed 24 weeks after EOT independently predicted de-novo HCC[55] (Tables 5 and 6).

Biochemical Surrogates of Advanced Liver Disease

Albumin and PLT were independently associated with HCC occurrence in two studies reporting data on F0-F3 patients.[37,38] Also, Watanabe et al found that low pre-treatment albumin values (<3.8 g/dl) increased the risk of HCC[49] (Tables 5–7).

Patient-Related Factors

Male gender and age independently predicted HCC occurrence also in CHC cohorts. Male gender was associated with de-novo HCC in 5[40,50,55,59,60] studies, and age in 7[40,41,48,52,53,55,58] (Table 5). Although age was analysed as a continuous variable in multivariate analysis, different cut-offs were associated with increased risks of HCC (>60, >62, >75 years). Race still emerged as independent predictor of de-novo HCC in the large US cohorts,[34,41] but was not confirmed by other studies. Co-morbidities influenced HCC development also in CHC cohorts: Kanwal et al reported that the presence of DM was independently associated with HCC occurrence,[34] whereas other studies found that altered γGT and ALT values predicted post-SVR HCC,[40,55] likely mirroring the presence of underlying metabolic disorders (Tables 5 and 6).

Genetic Predictors

In CHC patients, two genetic factors were independently associated with HCC occurrence. Nagata et al found that IL28B rs8099917 polymorphism (non-TT) was associated with an increased risk of HCC in a large cohort of 752 patients followed-up for 1.8 years.[54] Conversely, the Japanese study by Iio et al reported that patients carrying the TLL1 rs17047200 AT/TT genotypes had significantly higher CumI of HCC, although T allele was associated with lower PLT and higher FIB-4 values.[47] In 348 F0-F3 patients from Italy, TLL1 genotype did influence HCC risk[26] (Table 5).

Alpha-Fetoprotein

Baseline αFP was independently associated with de-novo HCC in 4 studies, which however identified different cut-offs: >4.6 ng/mL ≥8 ng/mL and ≥10 ng/mL[42,47,55,57] (Table 5). In addition, some authors investigated the predictive values of post-treatment αFP (Table 5): values at both EOT,[50–52,59] and SVR12[48,58,60] time-points were associated with de-novo HCC. At SVR12, the following cut-offs were identified: >5 ng/mL, >6.5 ng/mL, ≥6 ng/mL. Interestingly, Watanabe et al proposed two different cut-offs (ROC analysis) for post-treatment αFP according to patient gender: >6.0 ng/mL in females and >3.5 ng/mL in males, respectively[59] (Tables 5 and 6).

Virus-Related Factors

The only study reporting a role of virus-related factors is the one by Kanwal et al, finding an association between HCV genotype 3 and de-novo HCC.[41]

Combined Scores

In the setting of CHC patients, 4 studies developed scores based on multiple variables to predict de-novo HCC, mostly assessed at EOT or SVR time-points. Hiraoka et al proposed the ADRES score, based on the combination of gender, FIB-4 and αFP assessed at SVR24, while Tani et al incorporated EOT-αFP (>6 ng/mL) and age (>75 years)[52,60] (Table 7). Iio et al combined SVR24- αFP and FIB-4 with the TLL1 genotype,[47] while Watanabe et al proposed two different models, either pre-DAA (including FIB-4, albumin and gender) or post-DAA (incorporating EOT- FIB-4 and αFP values)[50] (Table 7).

Predictors of Recurrent HCC

The risk of HCC following antiviral treatment was strongly influenced by previous HCC history. Not only rates of recurrent HCC were significantly higher than those of de-novo HCC (Tables 2, 4, 5 and 8), but previous HCC history was the strongest predictor of HCC development in cohorts analysing cumulative data from patients with and without pre-DAA liver cancer. Rates of HCC recurrence following DAA were similar[18,19,23,61] or even lower[62] than those reported in untreated patients, and most authors reported that oral antivirals did not enhance the risk of recurrence.[12,15,18,19,23,61]

Table 8 Characteristics of Studies Reporting Data on HCC Recurrence

Author	Enrollment Period	Study Design	Patients	Males	Age	Fibrosis	CPT Score	SVR	HCC (Number)	Follow-Up
Cirrhosis (n=12)										
Conti, 2016[8]	Italy 2015	Multicenter, retrospective	59	40 (68%)	72 (48–84)	LSM 23.6 ± 1.39	CPT-A 49 CPT-B 10	53 (90%)	17 (29%) SVR 15 CPT-A 12	24 w°°
Pol, 2016[23]	France 2012–2014	Multicenter, retrospective,	13 (CIRVIR)	11 (85%)	61 ± 10	NA	CPT-A 13*	13 (100%)	1 (7.7%)	16. 5 (12.7–32.2) m
Zavaglia, 2017[72]	Italy	Multicenter, retrospective	31	20 (65%)	65 ± 8	NA	CPT-A 25 CPT-B 6	26/27 (96.3%)	1 (3.2%)	8 (P25-P75:5–10.9) m°
Virlogeux, 2017[61]	France 2009–2016	Single-center retrospective,	23	20 (87%)	58 (51–84)	NA	CPT-A 20 CPT-B 3	22 (96%)	11 (47.8%) CPT-A 9	NA
Cabibbo, 2017[13]	Italy 2015–2016	Multicenter, prospective	143	86 (60%)	70 ± 9	NA	CPT-A 123 CPT-B 20	138 (96%)	29 (20.3%)	8.7 (3–19) m°°
Ravaioli, 2018[25]	Italy 2015–2016	Single-center, retrospective	19	NA	NA	NA	NA	NA	7 (36.8%)	15 (12–19)°°ç
Degasperi, 2019[22]	Italy 2014–2016	Single-center, longitudinal	60	37 (62%)	72 (51–86)	LSM 24.4 (13.1–33.3)	CPT-A 52 CPT-B 8	97%ç	20 (33%) SVR 19	25 (3–39) m°
Lleo, 2019[28]	Italy 2015	Multicenter, longitudinal	161	111 (70%)	151 (94%) ≥50years	53 (33%) LSM ≥25 kPa	CPT-A 137 CPT-B/C 22	153 (95%)	38 (23.6%) SVR 34 CPT-A 35	NA
Kwon, 2019[51]	Korea 2015–2017		28	NA	NA	NA	NA	22/24 (91.7%)	5 (17.9%) SVR 5	1y°°ç
Casadei-Gardini, 2019[29]	Italy 2015–2016	Multicenter, Retrospective	98	60 (61.2%)	71 (47–86)	NA	CPT-A 72 CPT-B 26	NA	30 (30.6%)	18.0 (0.4–26.4) m°ç
Degasperi, 2020[31]	Italy 2014–2016	Single-center, retrospective	57	36 (63%)	72 (51–86)	LSM 21.0 (12.0–36.3) FIB-4 6.0 (1.1–22.4)	CPT-A 49 CPT-B 8	96%ç	28 (49%) CPT-A 25	43 (3–57) m°

(*Continued*)

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Table 8 (Continued).

Sangiovanni, 2020[32]	Italy	Multicenter, prospective	124	85 (69%)	73 (46–86)	NA	CPT-A 112 CPT-B 12	118 (95%)	40 (32%) SVR 36	16 (5–31) m[°]
Any Fibrosis Stage or not specified (n=12)										
Reig, 2016[7]	Spain 2014–2015	Multicenter, retrospective	58	40 (69%)	66 (45–83)	NA	55 (95%) (CPT-A 50) (CPT-B 3) (CPT-C 2)	39/40 (97.5%)	16 (27.6%) F4 15 CPT-A 11 CPT-B 2 CPT-C 1	5.7 (0.4–14.6) m[°°]
Torres, 2016[63]	US 2010–2015	Single-center prospective	8	7 (88%)	64 (57–87)	NA	7 (88%) (CPT-A 3) (CPT-B 4)	6 (75%)	0	12 (4–60) m[°°]
Pol, 2016[23]	France 2012–2014	Multicenter, retrospective	189 (HEPATHER)	147 (78%)	62 ± 9	NA	152 (80%)	148 (91.9%)	24 (12.7%)	20.2 m[°]
Kolly, 2017[64]	Europe	Multicenter, retrospective	47	76%	60 (48–78)	NA	40 (85%) CPT-A 80%	NA	NA	9.6 m[°°]
Tachi, 2017[56]	Japan 2014–2015	Multicenter, prospective	30	NA	NA	NA	NA	30 (100%)	12 (40%)	18.1 (5.6–31.2) m[c]
Ikeda, 2017[62]	Japan 2014–2016	Single-center, retrospective	177	106 (60%)	71 (39–87)	NA	NA	155/173 (90%)	61 (34.5%)	20.7 (7.0–26.2) m[°]
Nagata, 2017[54]	Japan 2014–2017	Multicenter, retrospective	83	NA	NA	NA	NA	NA	22 (27%)	2.3 y
Ogawa, 2018[38]	Japan 2015–2016	Multicenter	152	81 (53%)	74 (66–79)	NA	90 (59%) CPT-A 100%	152 (100%)	26 (17%)	17 (1–23) m[°c]
Kogiso, 2018[65]	Japan 2014–2018	Single-center retrospective	45	32 (71%)	69 (48–82)	FIB-4 5.33 (1.64–15.40)	15 (33%) CPT A5-B8	43 (96%)	15 (33%) SVR 14 F4 15	25.9 (2.7–41.3) m[°]

Nakano, 2019[66]	Japan 2015–2017	Multicenter	459	269 (59%)	75 ± 8	FIB-4 7.10 ± 4.16 APRI 2.32 ± 1.81	323 (70%)	459 (100%)	217 (47.2%)	29.4 ± 6.8 m°
Zou, 2019[67]	US 2015–2017	Multicenter, retrospective	264	261 (99%)	66 ± 5	NA	222 (84%) CPT-A 172 CPT-B 46 CPT-C 4	244 (92%)	69 (26.1%) F4 69	23.3 (±9.9) m°
Ahn, 2020[68]	South Korea 2015–2016	Multicenter, retrospective	100	67 (67%)	69 ± 8	NA	79 (79%) (CPT-A 74) (CPT-B 4) (CPT-C 1)	88 (88%)	37 (37%) F4 32 CPT-A 35 CPT-B 1 CPT-C 1	15.8 (4.4–29.9) m°

Notes: Values are expressed as median (range), mean ± standard deviation and/or percentages (%). Age is calculated in years-old; LSM is calculated in kPa. LSM by FibroScan®. °From DAA start; °°From EOT. *Only CPT-A patients included. [c]Available for patients with and without HCC history.

Abbreviations: HCC, hepatocellular carcinoma; F4, cirrhosis; SVR, sustained virological response; LSM, liver stiffness measurement; CPT, Child-Pugh-Turcotte score; w, weeks, m, months; y, years; P, percentile; FIB-4, fibrosis-4 index; APRI, AST to platelet ratio index; US, United States.

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Rates of HCC recurrence ranged between 3.2% and 49%, with one study only[63] reporting no recurrence however among 8 patients (7 with cirrhosis) (Table 8). Almost all studies tried to identify clinical predictors of HCC recurrence during variable follow-up, despite the inclusion of patients with different characteristics, including tumour burden (Tables 8 and 9). In two retrospective French studies, the authors found HCC predictors different from DAA use when comparing untreated vs DAA-treated patients.[23,61] Similarly, Ogawa et al were not able to identify predictive factors of HCC recurrence in 62 F0-F3 patients with an SVR, whilst other studies on CHC patients did not focused on the sub-group of non-cirrhotics.[38] In most cases, data were obtained from cohorts including both SVR and non-SVR patients; 4 studies enrolled only cured patients, whilst this information was lacking in other 4. When reported, rates of treatment failure ranged between 2.5% and 25% (Table 8). In 12 studies all patients had a diagnosis of cirrhosis, and most of them (n=9) included also decompensated (CPT-B) patients (Table 8). In studies enrolling CHC patients, rates of cirrhosis ranged between 33% and 95% (n=9) or were not reported (n=4), and only few authors (n=4) reported information on fibrosis stage in patients with a complete response (CR) to previous HCC who subsequently developed HCC recurrence (Table 8).

Severity of Liver Disease

Despite the inclusion of cirrhotic patients in CHC studies, only one of them was able to identify cirrhosis as an independent risk factor for HCC recurrence.[38] Although not reported in most cases, expected high rates of cirrhosis in patients developing recurrent HCC might have attenuated the weight of this variable. However, further reinforcing the strength of liver disease severity as HCC predictor, some authors found that indirect markers of fibrosis were independently associated with HCC recurrence. For example, Conti et al reported that baseline LSM independently predicted HCC in 59 cirrhotics followed-up for 24 weeks,[8] whereas Nagata et al found that WFA*M2BP assessed at SVR24 predicted HCC recurrence in 83 CHC patients[54] (Table 9).

Patient-Related Factors

According to published studies, patients' characteristics had low impact on HCC recurrence, as only few authors found that they were independently associated with recurrent HCC following an SVR to DAA. However, both age[8,64] and, in cirrhotic patients, comorbidities such as DM[22,31] and alcohol[32] seemed to play a role in influencing HCC risk. Moreover, Degasperi et al reported that ethnicity (ie, Egyptian vs Italian) was an independent risk factor for HCC recurrence in their European cohort[22] (Tables 6 and 9).

Tumour Burden

Rates of HCC recurrence were strongly influenced by tumour burden in most studies analysing either F4 or CHC cohorts (Table 9). One of the most important predictors of HCC recurrence was history of HCC recurrence before DAA[8,13,32] together with the number of HCC treatments finally leading to CR achievement before anti-HCV therapies.[62,65,66] In addition, time elapsing between prior HCC treatment and DAA start was significantly associated with an increased risk of recurrent HCC in several studies,[38,64,67,68] where patients treated for HCC less than one year prior to DAA exhibited an increased risk of tumour recurrence.[38,68] Lastly, some authors reported that also prior HCC size,[13] number of nodules[38] and type of HCC treatment (ie, palliative vs curative)[38,67] were independently associated with HCC recurrence, although these data were not confirmed by others[8,22,65] (Table 6). However, these results should be cautiously interpreted, as they are strongly influenced by study design and patients enrollment; recently, an individual patient-data meta-analysis pooling data of 977 patients from 21 studies have further enhanced the importance of pre-DAA HCC history and tumour burden.[19]

HCC Biomarkers

Four studies found that higher baseline (DAA start) values of αFP were independently associated with HCC recurrence.[19,28,54,66] Casadei-Gardini and others found that aspartate aminotransferase to lymphocyte ratio (ALRI), which had been previously proposed for inclusion in HCC surveillance algorithms,[69] independently predicted HCC recurrence in 98 cirrhotic patients (73% CPT-A) treated with DAA 8.5 months after CR[29] (Tables 6 and 9).

Conclusions

Despite the expected decrease in HCC burden,[70] the widespread use of DAA to cure HCV infection will finally lead large cohorts of SVR patients to be maintained under surveillance. In fact, the number of patients requiring HCC surveillance due to pre-treatment advanced fibrosis is expected to increase over time, as a consequence of worldwide diffusion of HCV screening and treatment programs.[71] Therefore, we are going to face with larger, ageing population still at risk of

Table 9 Incidence and Factors Associated with HCC Recurrence

Author	SVR Status	Incidence of HCC (CumI)							Independent Predictors	Time to HCC Recurrence (From DAA)
		CumI						100 PY		
		6-Month	1-Year	1.5-Year	2-Year	3-Year	4-Year			
Cirrhosis (n=11)										
Conti, 2016[8]	SVR + non-SVR	3.1%	–	–	–	–	–	–	Age, LSM	NA
Pol, 2016[23]	SVR	–	–	–	–	–	–	1.11 PM	–	16.5 (12.7–32.2) m
Zavaglia, 2017[72]	SVR + non-SVR	–	–	–	–	–	–	–	NA	8 m
Virlogeux, 2017[61]	SVR + non-SVR	–	–	–	–	–	–	1.7 PM	None***	13.0 (3.0–24.7) m°
Cabibbo, 2017[13]	SVR + non-SVR	12%	26.6%	29.1%	–	–	–	–	HCC size, prior HCC recurrence	NA
Ravaioli, 2018[25]	SVR + non-SVR	–	–	–	–	–	–	–	NA	10 (6–15)°°
Degasperi, 2019[22]	SVR + non-SVR	7.0%	17%	27%	43%	43%	–	–	DM	23 (7–37) m°
Lleo, 2019[28]	SVR + non-SVR	8.5%	20.9%	26.9%	–	–	–	–	Non-SVR, αFP ≥10 ng/mL	NA
Casadei-Gardini, 2019[29]	SVR + non-SVR	0.074*	0.261*	0.380*	–	–	–	–	ALRI	19.2 (1.1–26.44) m°
Degasperi, 2020[31]	SVR + non-SVR	–	–	–	–	–	51%	–	DM, ethnicity	NA
Sangiovanni, 2020[32]	SVR + non-SVR	–	–	–	42.9%	–	–	29.9	Alcohol, prior HCC recurrence	NA
Any Fibrosis Stage or not specified (n=10)										
Reig, 2016[7]	SVR + non-SVR	–	–	–	–	–	–	–	NA	3.5 (1.1–8) m°
Pol, 2016[23]	SVR + non-SVR	–	–	–	–	–	–	0.73 PM	None***	NA

(*Continued*)

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Table 9 (Continued).

Kolly, 2017[64]	NA	4%	19%	–	42%	–	–	–	Age, time HCC Tx–DAA	NA
Ikeda, 2017[62]	SVR + non-SVR**	9.6**	30.1%**	–	39.6%**	–	–	–	Number of prior HCC Tx	NA
Nagata, 2017[54]	SVR + non-SVR**	–	–	–	–	22.9%**	–	–	**Pre-DAA:** αFP **SVR24:** WFA*M2BP°°	2.3 y
Ogawa, 2018[38]		–	**Overall** NA **F0-F3** 6.5% **F4** 23.1%	–	–	–	–	–	**Overall:** Cirrhosis, time HCC Tx-DAA <1 year, nodules ≥2, palliative HCC Tx **F0-F3:** None **F4:** Time HCC Tx-DAA <1 year, palliative HCC Tx	NA
Kogiso, 2018[65]	SVR	–	–	–	–	–	–	–	Number of prior HCC Tx	11.6 (2.2–34.2) m°°
Nakano, 2019[66]	SVR	–	27.1%	–	43.6%	51.1%	–	–	αFP, number of prior HCC Tx	34 m°°°
Zou, 2019[67]	SVR + non-SVR	–	3.3%	–	20.3%	–	–	3.8	Palliative HCC Tx, Time HCC Tx-DAA, non-SVR	12.2 ± 8 m°
Ahn, 2020[68]	SVR + non-SVR	–	28.4%	–	61.3%	–	–	–	Last HCC Tx <1 year	NA

Notes: °From DAA start; °°From EOT; °°°From SVR12. *Cumulative Hazards of HCC recurrence; **CumI are available for SVR patients, only (vs predictors of HCC); ***comparison between untreated vs DAA-treated CR patients. **Abbreviations:** HCC, hepatocellular carcinoma; CumI, cumulative incidence; DAA, direct-acting antivirals; LSM, liver stiffness measurement; F4, cirrhosis; CHC, chronic hepatitis C; NA, not available; PM, person/month; w, weeks, m, months; y, years; ALRI, AST to lymphocyte ratio; αFP, alpha-fetoprotein; DM, diabetes mellitus; WFA*M2BP, *Wisteria floribunda* agglutinin positive Mac-2 binding protein; tx, treatment; DAA, direct-acting antivirals; CR, complete response.

HCC, although HCC risk is lower than that reported in active HCV infection. As a consequence, the investigation of HCC predictors is of paramount importance in order to better optimize surveillance strategies, with the ultimate goal of personalized follow-up algorithms. While advanced fibrosis and cirrhosis represent strong predictors of HCC development, either de-novo or recurrent, literature data suggest that many co-factors may contribute to the oncogenic risk. While some of these factors are modifiable or can be potentially improved by successful antiviral treatments (fibrosis, portal hypertension), others are only partially modifiable (metabolic syndrome) or not modifiable at all (aging, HCC history). Due to the complex interactions and competing risks resulting from these variables, combination analyses or composite scores are those expected to better improve prediction capability, with all the challenges related to large-scale applicability in heterogeneous patient populations. Therefore, in most cases prospective validation in larger cohorts is still needed.

Disclosure

Roberta D'Ambrosio reports being on the advisory board for AbbVie and MSD; speaking and teaching for AbbVie, Gilead and MSD; and research support from AbbVie, Gilead and MSD, outside the submitted work. Elisabetta Degasperi reports personal fees from ABBVIE and grants, personal fees and non-financial support from GILEAD, outside the submitted work.The authors report no conflicts of interest in this work.

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