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ORIGINAL ARTICLE

HCC incidence after hepatitis C cure among patients with advanced fibrosis or cirrhosis: A meta-analysis

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Abstract

Background and Aims: HCV cure reduces but does not eliminate the risk of HCC. HCC surveillance is recommended in populations where the incidence exceeds 1.5% per year. In cirrhosis, HCC surveillance should continue after HCV cure, although it is uncertain if this should be indefinite. For patients with advanced fibrosis (F3), guidelines are inconsistent in their recommendations. We evaluated the incidence of HCC after HCV cure among patients with F3 fibrosis or cirrhosis.

Approach and Results: This systematic review and meta-analysis identified 44 studies (107,548 person-years of follow-up) assessing the incidence of HCC after HCV cure among patients with F3 fibrosis or cirrhosis. The incidence of HCC was 2.1 per 100 person-years (95% CI, 1.9–2.4) among patients with cirrhosis and 0.5 per 100 person-years (95% CI, 0.3–0.7) among patients with F3 fibrosis. In a meta-regression analysis among patients with cirrhosis, older age (adjusted rate ratio [aRR] per 10-year increase in mean/median age, 1.32; 95% CI, 1.00–1.73) and prior decompensation (aRR per 10% increase in the proportion of patients with prior decompensation, 1.06; 95% CI, 1.01–1.12) were associated with an increased incidence of HCC. Longer follow-up after HCV cure was associated with a decreased incidence of HCC (aRR per year increase in mean/median follow-up, 0.87; 95% CI, 0.79–0.96).

Conclusions: Among patients with cirrhosis, the incidence of HCC decreases over time after HCV cure and is lowest in patients with younger age and compensated cirrhosis. The substantially lower incidence in F3 fibrosis is below the recommended threshold for cost-effective screening. The results should encourage the development of validated predictive models that better identify at-risk individuals, especially among patients with F3 fibrosis.

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Abbreviations: aRR, adjusted rate ratio; DAA, direct-acting antiviral; IFN, interferon; SVR, sustained virologic response.

INTRODUCTION

With the introduction and widespread uptake of direct-acting antiviral (DAA) therapy for chronic HCV infection, the number of patients who have received HCV treatment has increased dramatically.[1] Almost all patients achieve a sustained virologic response (SVR), and most patients encountered in clinical practice in the coming years will have achieved HCV cure.[2]

After HCV cure, ongoing liver disease management is largely dictated by the residual risk of HCC, which is reduced but not eliminated by viral eradication.[3] The annual risk of HCC needed for surveillance to be cost-effective is generally accepted to be 1.5%,[4,5] although the development and validity of this threshold are debated.[6] For patients with cirrhosis, it is universally agreed that HCC risk is sufficient to justify ongoing surveillance after HCV cure. For patients with advanced fibrosis (F3), guidelines are inconsistent in their recommendations, likely reflecting challenges in accurate fibrosis staging and the uncertain cost-effectiveness of surveillance in this group.[7,8]

As the number of patients with HCV cure grows, it is important to refine which patients truly need ongoing HCC surveillance. Currently, it is uncertain if HCC risk declines over time after HCV cure and whether surveillance can ever be safely discontinued among patients with cirrhosis.[9] Additionally, it is unclear whether surveillance should be recommended to all patients with F3 fibrosis after HCV cure or reserved for those identified to be at high risk. A detailed analysis of HCC incidence over time, among patients with F3 fibrosis or cirrhosis after HCV cure, would inform such decisions. To our knowledge, there have been no published meta-analyses assessing HCC incidence among patients with F3 fibrosis or meta-regression analyses designed to explore clinical factors associated with HCC risk among patients with cirrhosis and HCV cure.

The aim of this systematic review was to evaluate the incidence of *de novo* HCC after HCV cure, among well-defined populations of patients with F3 fibrosis or cirrhosis. Meta-regression analyses were used to identify study-level factors associated with HCC risk.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[10] The study protocol was registered with PROSPERO (ID, CRD42021226955).

Eligibility criteria

We included prospective and retrospective studies, reporting HCC occurrence after HCV cure, if they met the following criteria:

a. Study population included defined populations of patients with F3 fibrosis and/or cirrhosis, with no prior history of HCC, who achieved HCV cure (following interferon [IFN]–based or DAA therapy).
b. HCC incidence was reported or could be derived in person-years after HCV cure.
c. The cohort size was at least 20 patients.
d. The mean/median follow-up after the end of HCV treatment was at least 12 months.

We only included studies with at least 12 months of follow-up because studies with shorter follow-up likely identify a high proportion of HCC cases already present before HCV treatment. We required studies to define cirrhosis using liver biopsy, liver elastography, clinical or imaging features of cirrhosis, and/or a history of hepatic decompensation. F3 cohorts were defined using liver biopsy or elastography. Studies using laboratory results to define fibrosis stage (e.g., aspartate aminotransferase to platelet ratio index or Fibrosis-4) were excluded. Studies also including patients with milder liver fibrosis (≤F2), a history of HCC, or without HCV cure were only included if the incidence of *de novo* HCC could be derived for patients with F3 fibrosis and/or cirrhosis and HCV cure. Studies only evaluating liver fibrosis after the start of HCV treatment or not appropriately designed to assess HCC development over time after HCV cure were excluded (labeled “unsuitable study design”). When it was unclear if patients had a history of HCC before HCV treatment, the authors were contacted; and if the authors did not confirm the absence of prior HCC, the study was excluded.

Information sources and search

We searched bibliographic databases, including MEDLINE (PubMed), Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL), using search terms related to HCV, liver fibrosis or cirrhosis, HCV cure, and HCC (Table S1), without time or language restrictions. Presentations at the International Liver Congress and The Liver Meeting were searched. Unpublished or ongoing studies were identified in ClinicalTrials.gov. Reference lists of articles included in the analysis and relevant review articles were hand-searched. Forward citation tracking was carried out using Scopus. Searches were performed in December 2020 and updated in October 2021.

Study selection

After duplicate removal, studies found through the primary search were screened by title and abstract. The full texts of potential studies were reviewed, and eligible studies were selected for inclusion (Figure 1). In the

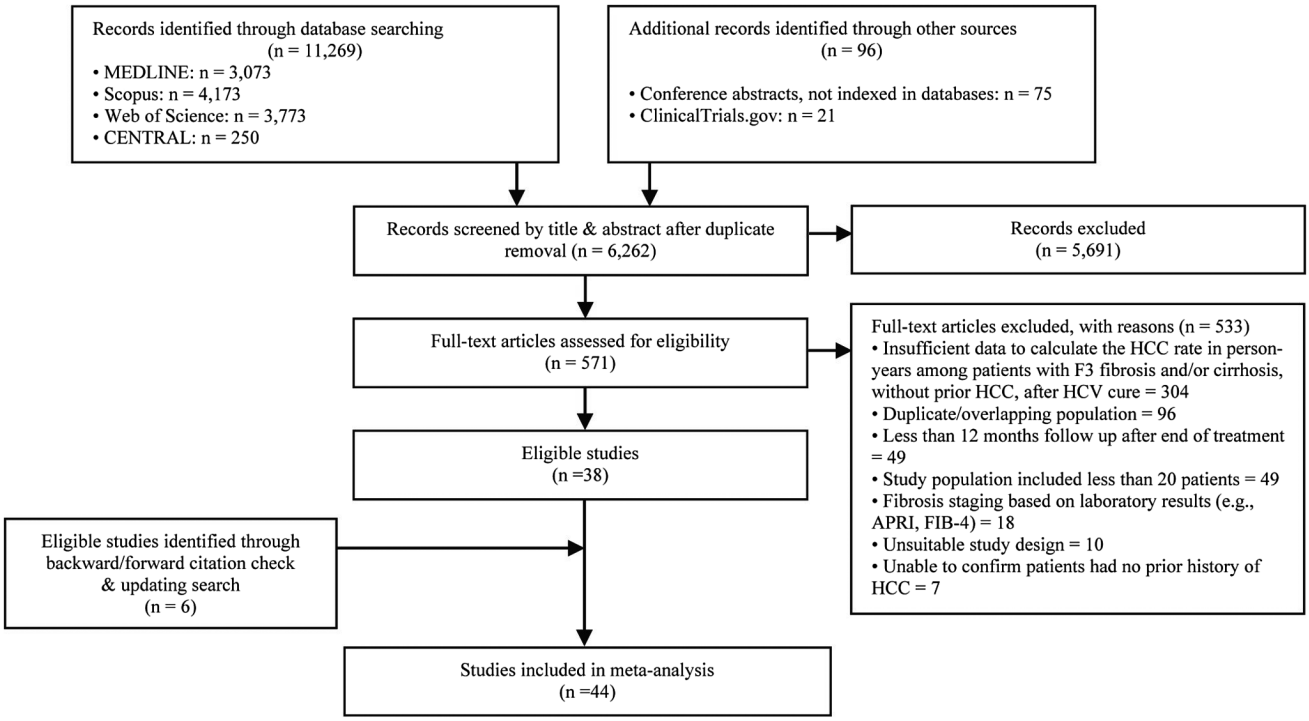

FIGURE 1 Flow diagram detailing the review process. Abbreviations: APRI, aspartate aminotransferase to platelet ratio index; FIB-4, Fibrosis-4

case of multiple publications from the same cohort, the one with the most up-to-date data was included. Where studies had overlapping populations, only the most representative study (e.g., most recent, largest person-years follow up, most comprehensive data, separate incidence rates available for patients with F3 fibrosis and cirrhosis) was selected.

Data collection process and data items

Required data were extracted into a standardized spreadsheet. Included items related to study design and setting, definition of liver fibrosis, patient characteristics, HCV treatment, follow-up, and occurrence of HCC. All data were specific to patients with F3 fibrosis and/or cirrhosis, without prior HCC, who achieved HCV cure. We did not accept the extrapolation of data from larger groups (e.g., where the patients of interest were a subgroup of a larger cohort, including some patients with prior HCC or without SVR). Authors were contacted if additional data were needed.

Risk of bias in individual studies

The risk of bias for the included studies was assessed using a modified scale derived from the Newcastle-Ottawa quality assessment scale for cohort studies.[11] This scale included six items with a total score of 8 (Table S2). Items assessed in the scale included diagnostic criteria for F3 fibrosis and cirrhosis, confirmation of HCV cure, how prior HCC was excluded, as well as the assessment for HCC (surveillance and diagnosis) and adequacy of follow-up. Studies with a score ≤4, 5–6, and ≥7 were considered to have high, moderate, and low risk, respectively.

Two reviewers (I. L., M. Y.) independently carried out title/abstract screening, full-text review, data extraction, and critical appraisal. Any discrepancies were discussed by the group to reach consensus.

Synthesis of results

The primary outcome was HCC incidence, overall and by stage of liver fibrosis (i.e., F3 fibrosis vs. cirrhosis). For each study, HCC incidence was calculated using the reported number of HCC cases and person-years of follow-up. The incidence among patients in each group (i.e., F3 fibrosis, cirrhosis, or combined F3–F4) was calculated only when the person-years of follow-up was reported or could be calculated, specifically for patients in the respective group. A fixed continuity correction of 0.5 was applied in studies with no HCC cases. Incidence of HCC was calculated per 100 person-years. Log transformation rates were used in all analyses, and the standard error of the log rate was calculated as the inverse of the square root of case counts and back-transformed for reporting. Heterogeneity across studies was assessed using the I^2

statistic, with an I^2 < 25%, 25%–75%, and >75% considered as low, moderate, and high heterogeneity, respectively.[12] Meta-analyses, stratified by the stage of liver fibrosis (F3 fibrosis, cirrhosis, or combined F3–F4), were undertaken to cumulate incidence estimates, using a random-effects model. Meta-analyses were also performed to explore the HCC incidence among patients with cirrhosis, stratified by the proportion of patients with a history of hepatic decompensation. Additional meta-analyses were conducted to cumulate incidence estimates (F3 fibrosis, cirrhosis), with analysis restricted to studies where all patients achieved HCV cure with either IFN-based or DAA therapy and with analysis stratified by the mean/median length of follow-up (<2 years vs. ≥2 years).

Study-level factors associated with HCC incidence were explored using meta-regression analyses, with covariates selected *a priori*, including age, gender, prior hepatic decompensation, HCV treatment (IFN-based vs. DAA therapy), HCV genotype, HBV and HIV coinfections, diabetes, follow-up duration, study design, study setting (single-center or multicenter), geographical setting (Europe, East Asia, or other), start of follow-up (start of treatment vs. end of treatment or later), and risk of bias scores. In studies with unavailable data of the proportion of patients with a history of decompensation, the proportion with Child-Pugh class B or C liver disease was used. The final adjusted model included variables with $p < 0.10$ in unadjusted analyses (0.10 was used as the p value cutoff to avoid model instability). Sensitivity analyses were performed to assess the possible collinearity between prior hepatic decompensation and HCV treatment (IFN-based or DAA therapy) in meta-regression models, given that patients with a history of decompensation are usually ineligible for IFN-based therapy. Additional sensitivity analyses were performed, excluding studies that relied on data linkage to identify patients and determine baseline characteristics. Publication bias was assessed using funnel plots and the Egger test. Statistical significance was assessed at $p < 0.05$ (p values are two-sided). All analyses were performed using Stata 17.0 (StataCorp, College Station, TX).

RESULTS

Study selection

A total of 11,269 records in bibliographic databases and 96 records from other sources were identified in the initial search. Following the full-text review of 571 records and an updated search, 44 studies were included in the analysis (Figure 1).

Study characteristics

Forty-four studies[13–57] with a total 35,739 patients and 107,548 person-years follow-up were included (Tables 1–3). Thirty-six studies (29,444 patients, 91,049 person-years follow-up) had required data for calculating HCC incidence among patients with cirrhosis (Table 2), with cirrhosis defined by histopathology (n = 7) or a combination of histopathology, liver stiffness measurement, imaging, or clinical features of cirrhosis (n = 29) (Table S3). Eight studies (2201 patients, 6851 person-years of follow-up) allowed calculation of HCC incidence among patients with F3 fibrosis, with F3 fibrosis defined by histopathology (n = 2), liver stiffness measurement (n = 4), or either histopathology or liver stiffness measurement (n = 2) (Table 3). Six studies (4094 patients, 9647 person-years of follow-up) only contained data for combined cohorts of patients with F3 fibrosis or cirrhosis (combined F3–F4). Most studies included cohorts where all patients achieved HCV cure with either IFN-based (n = 18, 2807 patients, 16,109 person-years of follow-up) or DAA therapy (n = 19, 19,663 patients, 42,354 person-years follow-up), although the seven studies with a combination of IFN and DAA-induced HCV cure had higher person-years of follow-up (13,269 patients, 49,085 person-years) (Table 1). Follow-up assessment for HCC started at the commencement of HCV treatment in 18 studies and at the end of treatment or later in the remaining studies (n = 26).

Risk of bias within studies

The risk-of-bias assessment scores are shown in Table S4. The risk of bias was high in seven studies (score ≤4), moderate in 23 studies (score 5–6), and low in 14 studies (score ≥7).

Analysis of HCC incidence

To assess HCC incidence after HCV cure among all patients with F3 fibrosis or cirrhosis, we pooled all included studies (n = 44), irrespective of whether they contained cohorts with F3 fibrosis, cirrhosis, or combined F3 fibrosis and cirrhosis. The pooled HCC incidence estimate was 1.7 per 100 person-years (95% CI, 1.5–1.9; I^2 = 82.4%) (Figure S1).

Among patients with F3 fibrosis (eight studies, 2201 patients, 6851 person-years of follow-up), the pooled HCC incidence estimate was 0.5 per 100 person-years (95% CI, 0.3–0.7), with low heterogeneity among the studies (I^2 = 13.8%) (Figure 2A). For patients with cirrhosis (36 studies, 29,444 patients, 91,049 person-years of follow-up), the pooled HCC incidence estimate was 2.1 per 100 person-years (95% CI, 1.9–2.4), with moderate heterogeneity among the studies (I^2 = 69.3%) (Figure 2B). In stratified analysis by the risk of bias score, there was no significant difference in HCC incidence across each

TABLE 1 Cumulative summary characteristics of the studies included in the analysis

	All studies		F3 fibrosis		Cirrhosis	
	Study, *n* (%)	Person-years of follow-up	Study, *n* (%)	Person-years of follow-up[a]	Study, *n* (%)	Person-years of follow-up[b]
Cohort design						
Prospective	25 (57)	37,409	3 (38)	2179	21 (58)	27,334
Retrospective	17 (39)	68,381	4 (50)	3251	14 (39)	63,379
Retrospective/prospective	2 (5)	1758	1 (13)	1421	1 (3)	337
Single-center or multicenter						
Single-center	19 (43)	18,450	5 (63)	4299	16 (44)	13,270
Multicenter	25 (57)	89,098	3 (38)	2552	20 (56)	77,779
Geographical setting						
Europe	25 (57)	37,842	4 (50)	3658	20 (56)	27,240
East Asia	8 (18)	14,221	2 (25)	1178	7 (19)	12,643
Other	11 (25)	55,485	2 (25)	2016	9 (25)	51,166
HCV cure following:						
IFN-based therapy	18 (41)	16,109	3 (38)	3077	14 (39)	9848
DAA therapy	19 (43)	42,354	5 (63)	3775	16 (44)	35,316
IFN-based or DAA therapy	7 (16)	49,085	0 (0)	0	6 (17)	45,885
Start point of follow-up						
Start of treatment	18 (41)	34,634	1 (13)	210	15 (42)	29,647
End of treatment[c]	15 (34)	54,703	5 (63)	3322	14 (39)	51,382
SVR12–24	11 (25)	18,210	2 (25)	3320	7 (19)	10,020

[a]Person-years of follow-up is specific to patients with F3 fibrosis (8 studies).
[b]Person-years of follow-up is specific to patients with cirrhosis (36 studies).
[c]Follow-up started 180 days after the start of HCV treatment in one study.

risk-of-bias group, among patients with F3 fibrosis or cirrhosis (Tables S5 and S6). Additionally, funnel plots and Begg's test showed no significant evidence of publication bias (Figure S2).

Stratified analysis among patients with cirrhosis, by history of hepatic decompensation

Of studies providing data on HCC incidence among patients with cirrhosis, 32 (89%) reported the proportion of patients with a history of hepatic decompensation before HCV cure (28,986 patients, 89,883 person-years of follow-up). Studies were grouped according to whether they included no patients with prior decompensation (10 studies, 2044 patients, 8863 person-years of follow-up), a proportion with prior decompensation (19 studies, 26,520 patients, 80,154 person-years of follow-up), or only patients with prior decompensation (three studies, 422 patients, 866 person-years of follow-up). In stratified analysis, the pooled estimates of HCC incidence were 1.3 per 100 person-years (95% CI, 0.9–1.9; I^2 = 64.8%) in studies where all patients were compensated, 2.2 per 100 person-years (95% CI, 2.0–2.5; I^2 = 74.7%) in studies where a proportion had prior decompensation, and 3.1 per 100 person-years (95% CI, 2.0–4.8; I^2 = 12.5%) in studies where all patients had prior decompensation (Figure 3).

Analyses among studies where all patients achieved HCV with either IFN-based or DAA therapy

Restricting analysis to studies where all patients achieved HCV cure with IFN-based therapy, among patients with F3 fibrosis (three studies, 430 patients, 3077 person-years follow-up), the pooled HCC incidence estimate was 0.4 per 100 person-years (95% CI, 0.2–0.1.2; I^2 = 60.2%) (Figure S3A). For patients with cirrhosis (14 studies, 1892 patients, 9848 person-years follow-up), the pooled HCC incidence estimate was 1.5 per 100 person-years (95% CI, 1.0–2.1; I^2 = 66.0%) (Figure S3B).

Restricting analysis to studies where all patients achieved HCV cure with DAA therapy, among patients with F3 fibrosis (five studies, 1771 patients, 3775 person-years of follow-up), the pooled HCC incidence estimate was 0.5 per 100 person-years (95% CI, 0.3–0.8; I^2 = 0%) (Figure S4A). For patients with cirrhosis (16 studies,

TABLE 2 Design, setting, and summary statistics for studies reporting HCC incidence after HCV cure, among patients with cirrhosis

First author, year (country)	Study design, setting	Patients, *n*	Age, mean or median, years	Male	HBV	HIV
Abe, 2020 (Japan)[13]	Retrospective, multicenter	188	70	48%	0%	0%
Aleman, 2013 (Sweden)[14]	Prospective, multicenter	110	50	65%	0%	0%
Audureau, 2020 (France)[15]	Prospective, multicenter	434	59	63%	0%	0%
Bergna, 2021 (Italy)[16]	Retrospective, single-center[a]	577	64	58%	1.4%	0%
Bruno, 2007 (Italy)[17]	Retrospective, multicenter	124	53	73%	0%	0%
Cardoso, 2016 (Portugal)[18]	Retrospective, single-center[a]	54	59	70%	–	–
Cheinquer, 2010 (Brazil)[19]	Prospective, single-center	38	51	63%	0%	0%
D'Ambrosio, 2011 (Italy)[20]	Prospective, single-center	62	61	65%	0%	0%
Di Marco, 2016 (Italy)[21]	Prospective, single-center	108	58	69%	0%	0%
Fan, 2020 (multicountry)[22]	Prospective, multicenter[d]	1259	60	69%	0%	0%
Hedenstierna, 2016 (Sweden)[23]	Retrospective, single-center	180	54	69%	0%	0%
Howell, 2018 (Australia)[24]	Prospective, single-center[a]	281	58	70%	0%	0%
Hsu, 2021 (Taiwan)[25]	Retrospective, multicenter	898	59	48%	0%	0%
Iacobellis, 2011 (Italy)[26]	Prospective, single-center	24	59	67%	0%	0%
Ikeda, 2005 (Japan)[27]	Retrospective, multicenter	97	–	–	–	–
Innes, 2018 (Scotland)[28]	Retrospective, multicenter	857	49	75%	0%	0%
Ioannou, 2019 (USA)[29]	Retrospective, multicenter	9784	61	97%	1.8%	3.0%
Janjua, 2020 (Canada)[30]	Retrospective, registry[b]	718	59	67%	9.7%	6.1%
Ji, 2017 (China)[31]	Prospective, single-center	34	56	38%	0%	0%
Jung, 2016 (Korea)[32]	Retrospective, single-center	50	–	–	–	–
Kozbial, 2018 (Austria)[33]	Prospective, multicenter	393	58	62%	0%	0%
Kumada, 2021 (UK)[34]	Prospective, multicenter[e]	364	54	72%	0%	0%
Lleo, 2019 (Italy)[35]	Prospective, multicenter	1679	62	62%	0%	0%
Lusivika-Nzinga, 2019 (France)[36]	Prospective, multicenter	2779	58	65%	0%	0%
Mariño, 2019 (Spain)[37]	Retrospective, multicenter	1070	59	60%	0.9%	4.2%
Mettke, 2018 (Germany)[38]	Prospective, single-center[c]	158	59	55%	–	–
Mira, 2013 (Spain)[39]	Prospective, multicenter	43	42	86%	0%	100%
Morisco, 2021 (Italy)[40]	Prospective, multicenter	687	64	54%	0%	0%
Nabatchikova, 2020 (Russia)[41]	Prospective, single-center	229	54	49%	0%	0%
Ruiz, 2018 (Spain)[42]	Prospective, single-center[a]	226	–	–	–	–
Shiha, 2020 (Egypt)[43]	Prospective, single-center	1,734	56	54%	0%	0%
Shiha, 2020ii (Egypt)[44]	Prospective, single-center[f]	947	55	73%	0%	0%
Tanaka, 2020 (multicountry)[45]	Retrospective, multicenter	2911	69	41%	0%	0%
Velosa, 2011 (Portugal)[46]	Retrospective, single-center	39	47	77%	0%	0%
Yang, 2020 (multicountry)[47]	Prospective, multicenter	223	57	49%	0.4%	0%
Yu, 2006 (Taiwan)[48]	Ambispective, multicenter	85	–	–	0%	0%

Abbreviations: EOT, end of treatment; SOT, start of treatment.

[a]Abstract or brief report.

[b]Data linkage used to identify patients and determine their baseline characteristics.

[c]Follow-up duration and HCC cases updated from recent brief report.[49]

[d]"Gilead SVR cirrhotic cohort" included.

[e]"HCV Research UK registry cohort" included.

[f]"External validation cohort: National Liver Institute, Menoufia University" included.

Diabetes	Genotype 1	Prior decompensation	DAA	Start of follow-up	Follow-up, mean or median, years	Person-years of follow-up	HCC cases, *n*
23%	70%	0%	100%	SOT	3.8	721	19
15%	24%	0%	0%	SOT	5.4	589	6
17%	71%	0%	45%	EOT	1.9	832	19
17%	62%	11%	100%	SOT	4.3	2500	46
–	–	0%	0%	SOT	8.5	1055	7
–	78%	36%	100%	SVR	1.0	54	4
–	16%	0%	0%	EOT	2.7	102	1
–	21%	0%	0%	EOT	6.8	424	3
28%	62%	0%	0%	SOT	7.9	853	7
–	63%	17%	100%	SVR	2.8	3525	71
18%	36%	2%	0%	SVR	7.0	1467	14
–	51%	8%	74%	SVR	1.3	741	15
23%	48%	0%	0%	SVR	4.2	3811	78
–	29%	100%	0%	EOT	4.7	112	5
–	–	–	0%	EOT	3.2	305	4
9%	–	16%	32%	SOT	2.4	3172	46
35%	84%	24%	77%	180 days after SOT	3.9	38,636	850
29%	68%	50%	68%	EOT	3.1	2199	36
–	53%	100%	0%	SVR	3.5	117	5
–	–	–	0%	SOT	4.0	199	6
19%	85%	19%	100%	EOT	1.4	547	16
20%	53%	100%	100%	SOT	1.8	637	15
20%	68%	17%	100%	EOT	1.2	1952	41
21%	68%	13%	100%	SOT	3.0	8348	192
19%	80%	22%	100%	SOT	1.7	1830	56
23%	77%	15%	100%	SOT	3.0	441	9
–	33%	0%	0%	SOT	4.5	200	1
–	80%	7%	100%	SOT	2.4	1625	26
20%	74%	28%	100%	EOT	2.5	572	14
–	–	–	100%	SOT	1.4	324	12
24%	0%	25%	100%	EOT	1.9	3463	101
18%	0%	30%	100%	EOT	1.8	1624	43
22%	77%	6%	100%	SOT	4.5	7153	221
–	36%	0%	0%	EOT	7.1	277	1
23%	84%	10%	86%	SVR	1.4	305	8
–	–	–	0%	EOT	4.0	337	9

TABLE 3 Design, setting, and summary statistics for studies reporting HCC incidence after HCV cure among patients with advanced fibrosis and among patients with advanced fibrosis or cirrhosis (combined F3–F4)

First author, year (country)	Study design, setting	Advanced fibrosis (F3, F3–F4) definition	Patients, *n*	Age, mean or median, years	Male
F3 fibrosis					
Hedenstierna, 2016 (Sweden)[23]	Retrospective, single-center	LSM: 9.5–12.4 kPa or Biopsy: Metavir F3 and no clinical diagnosis of cirrhosis	219	51	59%
Ikeda, 2005 (Japan)[27]	Retrospective, multicenter	Biopsy: IASL F3	170	–	–
Jung, 2016 (Korea)[32]	Retrospective, single-center	Biopsy: Batts-Ludwig F3 and no clinical diagnosis of cirrhosis	41	–	–
Kozbial, 2018 (Austria)[33]	Prospective, multicenter	LSM: 9.6–12.4 kPa and no clinical diagnosis of cirrhosis	158	57	58%
Pereira Guedes, 2020 (Portugal)[50]	Retrospective, single-center	LSM: 9.6–12.4 kPa or Biopsy: Metavir F3 and no clinical diagnosis of cirrhosis	75	56	63%
Sánchez-Azofra, 2021 (Spain)[51]	Ambispective, multicenter	LSM: 9.5–14.5 kPa and no clinical diagnosis of cirrhosis[c]	506	57	60%
Shiha, 2020 (Egypt)[43]	Prospective, single-center	LSM: 10.3–16.3 kPa and no clinical diagnosis of cirrhosis[d]	638	55	49%
Shiha, 2020 (Egypt)[44]	Prospective, single-center[b]	LSM: 10.3–16.3 kPa and no clinical diagnosis of cirrhosis[d]	394	55	71%
Advanced fibrosis or cirrhosis (combined F3–F4)					
Cardoso, 2010 (France)[52]	Retrospective, single-center	Biopsy: Metavir F3	103	55	70%
Corma-Gómez, 2021 (Spain)[53]	Prospective, multicenter	LSM: ≥9.5kPa	972	–	–
Matsumura, 2013 (Japan)[54]	Prospective, single-center	Biopsy: IASL F3	50	55	64%
Morgan, 2010 (USA)[55]	Prospective, multicenter	Biopsy: Ishak ≥ 3	140	49	76%
Romano, 2018 (Italy)[56]	Prospective, multicenter	LSM: ≥10 kPa or Biopsy: Metavir F3	2637	–	–
van der Meer, 2012 (multicountry)[57]	Retrospective, multicenter	Biopsy: Ishak ≥ 4	192	–	–

Abbreviations: EOT, end of treatment; IASL, International Association for the Study of the Liver, 1994 staging system; LSM, liver stiffness measurement; SOT, start of treatment.

[a]Abstract or brief report.

[b]"External validation cohort: National Liver Institute, Menoufia University" included.

[c]Patients were excluded if they had radiological features of cirrhosis, a platelet count <120 × 10^9/L (<100 × 10^9/L for patients with HIV coinfection), or endoscopic evidence of varices.

[d]A clinical diagnosis of cirrhosis was made if more than one of the following criteria: clinical signs and laboratory parameters of cirrhosis (e.g., splenomegaly, albumin ≤ 3.5 g/dL, platelet count ≤ 100 mm^3), radiological features of cirrhosis, or LSM > 16.3 kPa.

15,255 patients, 35,316 person-years follow-up), the pooled HCC incidence estimate was 2.5 per 100 person-years (95% CI, 2.2–2.8; I^2 = 59.5%) (Figure S4B).

Stratified analyses by length of follow-up

Of studies providing data on HCC incidence among patients with F3 fibrosis, two (25%) had a mean/median follow-up <2 years (796 patients, 1368 person-years follow-up), and six (69%) had a mean/median follow-up ≥2 years (1405 patients; 5483 person-years follow-up). In stratified analysis, the pooled estimates of HCC incidence were 0.6 per 100 person-years (95% CI, 0.3–1.2; I^2 = 0%) in studies with a follow-up <2 years and 0.5 per 100 person-years (95% CI, 0.3–0.8; I^2 = 30.4%) in studies with a follow-up ≥2 years (Figure S5A).

Of studies providing data on HCC incidence among patients with cirrhosis, 11 (31%) had a mean/median follow-up <2 years (7405 patients, 12,309 person-years follow-up), and 25 (69%) had a mean/median follow-up ≥2 years (22,039 patients, 78,740 person-years follow-up).

HBV	HIV	Diabetes	Genotype 1	DAA	Start of follow-up	Follow-up, mean or median, years	Person-years of follow-up	HCC cases, *n*
0%	0%	6%	43%	0%	SVR	8.5	1899	3
–	–	–	–	0%	EOT	5.7	968	6
–	–	–	–	0%	SOT	5.1	210	2
0%	0%	12%	90%	100%	EOT	1.0	164	0
0%	0%	13%	67%	100%	EOT	2.3	175	2
0%	18%	17%	–	100%	SVR	2.8	1421	5
0%	0%	11%	0%	100%	EOT	1.8	1205	8
0%	0%	13%	0%	100%	EOT	2.6	811	3
0%	0%	17%	38%	0%	SOT	4.7	481	6
0%	–	–	–	–	SVR	3.3	3200	16
0%	–	–	44%	0%	SVR	8.0	400	4
–	–	–	72%	0%	SOT	7.2	1033	2
–	–	–	–	100%	SOT	1.2	3263	31
0%	0%	–	–	0%	SVR	6.6	1270	7

In stratified analysis, the pooled estimates of HCC incidence were 2.7 per 100 person-years (95% CI, 2.4–3.1; I^2 = 13.0%) in studies with a follow-up <2 years and 1.9 per 100 person-years (95% CI, 1.6–2.2; I^2 = 73.3%) in studies with a follow-up ≥2 years (Figure S5B).

Meta-regression

Meta-regression analysis was used to identify study-level factors associated with HCC incidence among patients with cirrhosis. In the adjusted meta-regression model, a higher mean/median age (adjusted rate ratio [aRR] per 10-year increased in age, 1.32; 95% CI, 1.00–1.73; p = 0.048) and a higher proportion of patients with prior decompensation (aRR per 10% increase in the proportion with prior decompensation, 1.06; 95% CI, 1.01–1.12; p = 0.028) were associated with increased HCC incidence (Table 4). Longer follow-up after HCV cure was associated with decreased HCC incidence (aRR per each year increase in mean/median follow-up, 0.87; 95% CI, 0.79–0.96; p = 0.007)

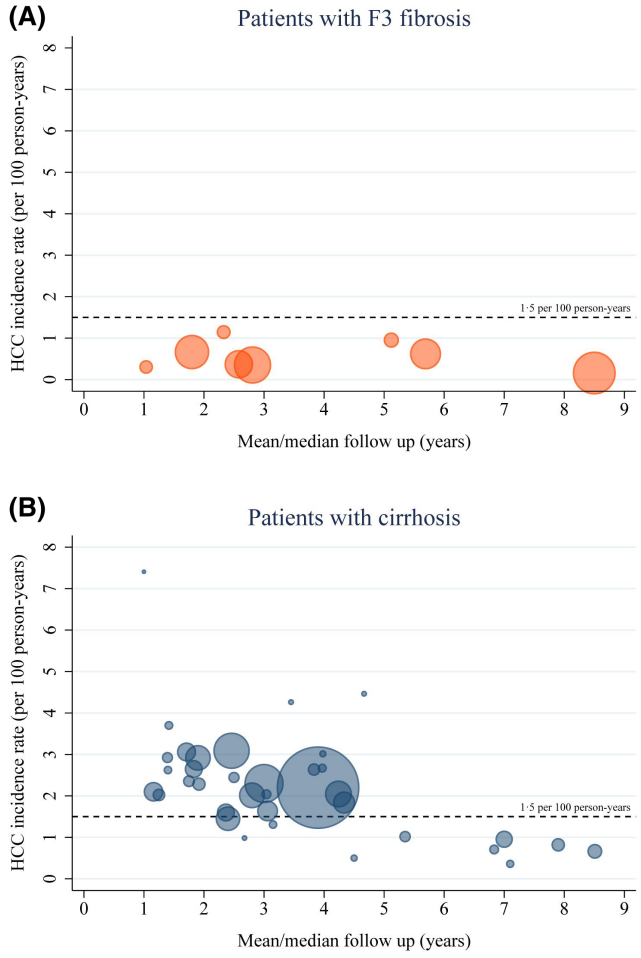

FIGURE 2 Forest plots of studies evaluating HCC incidence rates after HCV cure (A) among patients with F3 fibrosis and (B) among patients with cirrhosis

(Table 4 and Figure 4). Genotype before HCV cure, type of HCV treatment (IFN-based or DAA therapy), and geographical setting were not associated with HCC incidence in the adjusted meta-regression analysis (Table 4). The residual I^2 of the adjusted model was 34%.

Two sensitivity analyses were performed. First, the type of HCV treatment (IFN-based or DAA therapy) was removed from the model as patients with prior decompensation are typically ineligible for IFN-based treatments, with no major difference in the results (residual I^2 = 32%) (Table S7). In the second sensitivity analysis, which excluded a Canadian study using data linkage to identify patients and determine their baseline characteristics (2199 person-years follow-up),[30] mean/median age and prior decompensation both increased in significance, while heterogeneity decreased (residual I^2 = 18%) (Table S8).

Among patients with F3 fibrosis, no study-level factors were associated with HCC incidence in meta-regression analysis (Table S9).

DISCUSSION

As the number of patients with HCV cure continues to increase, it is important to identify which patients would benefit from ongoing HCC surveillance. Our study provides estimates of HCC incidence after HCV cure among patients with F3 fibrosis (0.5 per 100 person-years) and patients with cirrhosis (2.1 per 100 person-years). We also revealed that HCC risk decreased with each additional year of follow-up after HCV cure in patients with cirrhosis. Although surveillance decisions are not based on HCC incidence alone,[6] our results provide valuable data that should inform and refine future HCC surveillance analyses and recommendations.

The declining HCC risk over time has significant implications for patients with cirrhosis, who are currently recommended to have indefinite surveillance after HCV cure. Our findings suggest that there may be a subgroup of patients with cirrhosis who could step down to a less intensive surveillance program at some point after HCV cure. Potentially, these patients will be identifiable using predictive models being developed for use after SVR.[15,44,58,59] As HCC risk decreases over time, these models will need to be dynamic and incorporate changes in risk factors over time in order to provide precise risk estimates and individualized surveillance recommendations. The reason HCC risk declines over time probably relates to regression of liver fibrosis, which is a slow process after HCV eradication.[60–63] Although our results seem logical, it should be noted that data from the US Veterans Affairs health care system have not demonstrated declining HCC risk over time among all patients (IFN-based and DAA-therapy) after HCV cure.[9,29] We acknowledged that our finding of a declining incidence over time could be due to a selection bias favoring studies with longer follow-up. Our results should encourage further studies to evaluate HCC risk over time, using individual-level data from large multicenter cohorts with longer follow-up.

Consistent with previous studies, our meta-regression analysis showed that older age and history of decompensation are associated with HCC risk after HCV cure among patients with cirrhosis.[9,28,43] These factors are clearly important and should also be included in predictive models. The proportion of patients treated with DAA therapy was not associated with HCC risk in adjusted analysis, consistent with previous meta-analyses.[64] It should be noted that our study only identified five studies that included patients with HBV coinfection, with small patient numbers, and that conclusions about the impact on HBV coinfection are limited. Additionally, as patients had underlying cirrhosis, it is likely that most were taking HBV antiviral therapy throughout follow-up.

In the meta-regression analysis, baseline diabetes was not associated with HCC risk. Although some

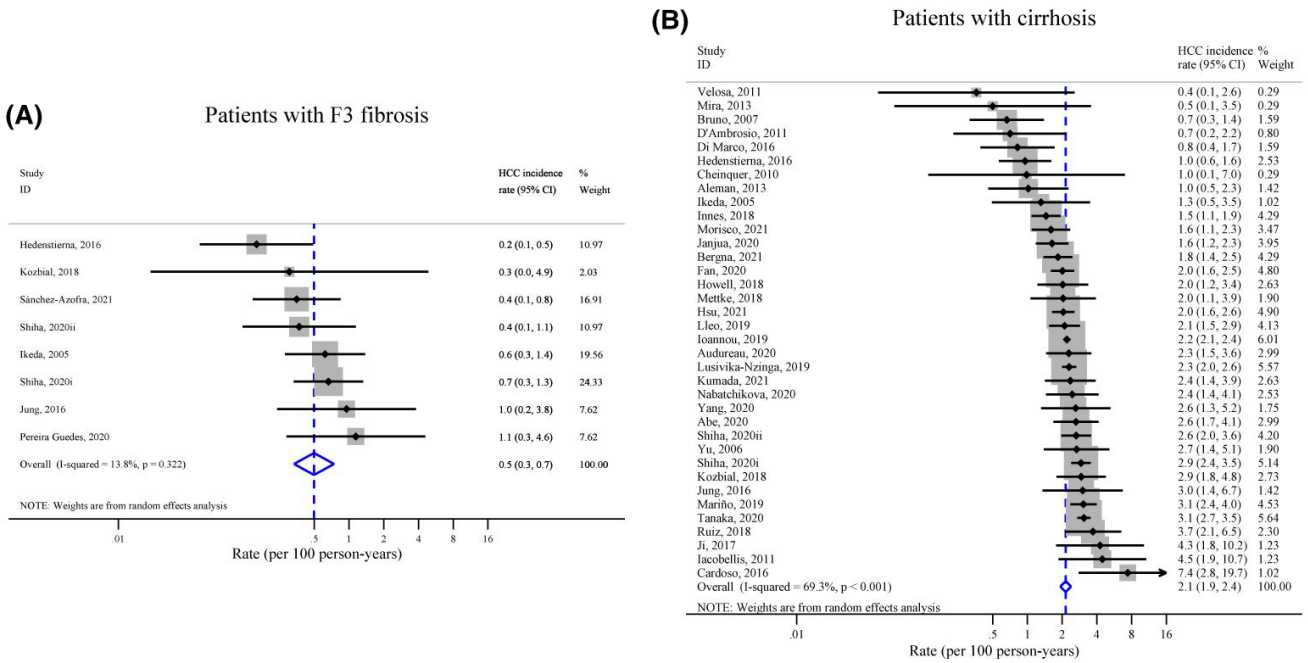

FIGURE 3 HCC incidence rates after HCV cure (A) among patients with F3 fibrosis and (B) among patients with cirrhosis

studies have shown the presence of diabetes at HCV cure to be associated with an increased HCC risk among patients with cirrhosis,[23,59] several larger studies from large cohorts have shown no relationship.[9,15,28,43] It is possible that HCV cure improves insulin resistance, mitigating any effect that baseline diabetes has on the occurrence of HCC.[65] More important is whether a patient has NASH during follow-up, with recent studies revealing genetic risk scores for hepatic fat accumulation; and steatohepatitis-related biomarkers are associated with the risk of *de novo* HCC after viral eradication.[59,66]

The low HCC incidence among patients with F3 fibrosis and HCV cure argues against universal surveillance of this group. Even using lower cost-effectiveness thresholds, such as the 1.32% estimated by a Markov model analysis after HCV cure or a more conservative threshold of 1% suggested by some authors, it seems unlikely that universal surveillance of this group would be cost-effective.[67,68] Of note, low heterogeneity in rates of HCC occurrence among patients with F3 fibrosis was observed across studies. However, it must be acknowledged that liver biopsy and elastography can misclassify patients, and some patients labeled as F3 fibrosis may truly have established cirrhosis.[69] Misclassification of cirrhosis, however, would have favored a higher incidence of HCC. We highlight that most studies included in our analysis had additional measures to exclude cirrhosis clinically. Indeed, our results are probably most relevant to patients classified as F3 fibrosis by liver biopsy or elastography (9.5 kPa or higher for all studies), who also have no clinical signs, laboratory parameters, or radiological features of cirrhosis. Although our results suggest that surveillance should not be offered to all patients with F3 fibrosis, some patients with F3 fibrosis would benefit from surveillance. We encourage the development of validated predictive models to better identify individuals with F3 fibrosis who should be offered surveillance.

Most systematic reviews assessing the impact of HCV treatment on HCC occurrence have compared SVR or HCV treatment to no SVR or no HCV treatment and often included patients with all stages of liver fibrosis.[70,71] Others have focused on comparing IFN-based to DAA therapy.[64] One meta-analysis did focus on patients with combined F3–F4 fibrosis and estimated a pooled HCC incidence of 1.05 per 100 person-years after IFN-induced SVR.[72] In contrast, the well-defined study populations in our current study allowed for a precise estimate of HCC incidence after HCV cure among patients with F3 fibrosis or cirrhosis. The considerable effort made to contact the authors and collect supplementary data is a major strength of this study, enabling meta-regression analyses, using data specific to cohorts of patients with F3 fibrosis or cirrhosis.

Although this study provides a comprehensive review of *de novo* HCC occurrence after HCV cure among patients with F3 fibrosis or cirrhosis, it does have several limitations. First, the start of follow-up assessment for HCC varied between studies, and studies starting at the commencement of HCV treatment likely report some HCC cases present before treatment. We highlight that the start of follow-up assessment (start of treatment vs. end of treatment or later) was

TABLE 4 Meta-regression analysis of factors associated with HCC incidence after HCV cure among patients with cirrhosis

	Number of studies	Unadjusted models		Adjusted model[a]	
		Rate ratio (95% CI)	*p*	Rate ratio (95% CI)	*p*
Mean/median age, per 10-year increase	32	1.36 (1.01–1.84)	0.046	1.32 (1.00–1.73)	0.048
Proportion of men, per 10% increase	32	0.90 (0.80–1.02)	0.091	0.97 (0.89–1.05)	0.391
Proportion of patients with a history of decompensation, per 10% increase	32	1.08 (1.01–1.15)	0.023	1.06 (1.01–1.12)	0.028
Proportion of patients cured with DAA therapy, per 10% increase	36	1.05 (1.02–1.08)	0.002	1.00 (0.96–1.04)	0.995
Proportion of patients with genotype 1 infection before HCV cure, per 10% increase	30	1.02 (0.96–1.08)	0.554		
Proportion of patients with genotype 3 infection before HCV cure, per 10% increase	20	0.90 (0.77–1.06)	0.198		
Proportion of patients with HBV coinfection, per 1% increase	31	0.98 (0.91–1.06)	0.621		
Proportion of participants with HIV coinfection, per 1% increase	31	0.99 (0.96–1.01)	0.273		
Proportion of participants with diabetes, per 10% increase	21	1.06 (0.81–1.39)	0.635		
Mean/median follow-up, per year increase	36	0.85 (0.79–0.91)	<0.001	0.87 (0.79–0.96)	0.007
Study design					
Prospective	21	1.00	0.581		
Retrospective/ambispective	15	0.92 (0.68–1.25)			
Single-center or multicenter					
Single-center	16	1.00	0.660		
Multicenter/registry	20	0.93 (0.68–1.28)			
Geographical setting					
Europe	20	1.00			
East Asia	7	1.36 (0.92–2.02)	0.122		
Other	9	1.18 (0.84–1.65)	0.336		
Start point for follow-up					
Start of treatment	15	1.00	0.542		
End of treatment or later	21	1.10 (0.81–1.49)			
Risk of bias score	36	0.98 (0.90–1.06)	0.526		

[a]Includes variables with $p < 0.1$ in unadjusted models (32 studies included); residual $I^2 = 34.06\%$.

not associated with HCC incidence in meta-regression analyses. Additionally, if follow-up started at SVR and all patients had imaging to exclude HCC at the time of SVR, the HCC incidence estimates would probably be lower. In the F3 fibrosis cohort this would have favored a lower incidence estimate, remaining well below the recommended threshold for cost-effective screening. Second, moderate heterogeneity in rates of HCC occurrence in patients with cirrhosis was observed across studies. The residual I^2 value was 34% in the adjusted meta-regression model and 18% after excluding one data-linkage study, indicating that factors included in the models explained most heterogeneity across studies. The residual heterogeneity is probably explained by other factors not considered in our analysis due to a lack of data, particularly alcohol-related liver disease and NASH. Although some studies reported the proportion of patients with a history of alcohol excess at HCV cure, the definition of alcohol excess varied considerably across studies, precluding its inclusion in our model. Third, our analysis only included baseline characteristics recorded at the time of curative HCV treatment. The presence of risk factors after HCV cure, including ongoing alcohol use, NASH, or the development of hepatic decompensation, would impact HCC risk. Again, our results should encourage further studies, using individual-level data from large multicenter cohorts to address these limitations.

In conclusion, this study demonstrates that HCC incidence in cirrhosis justifies cost-effective screening,

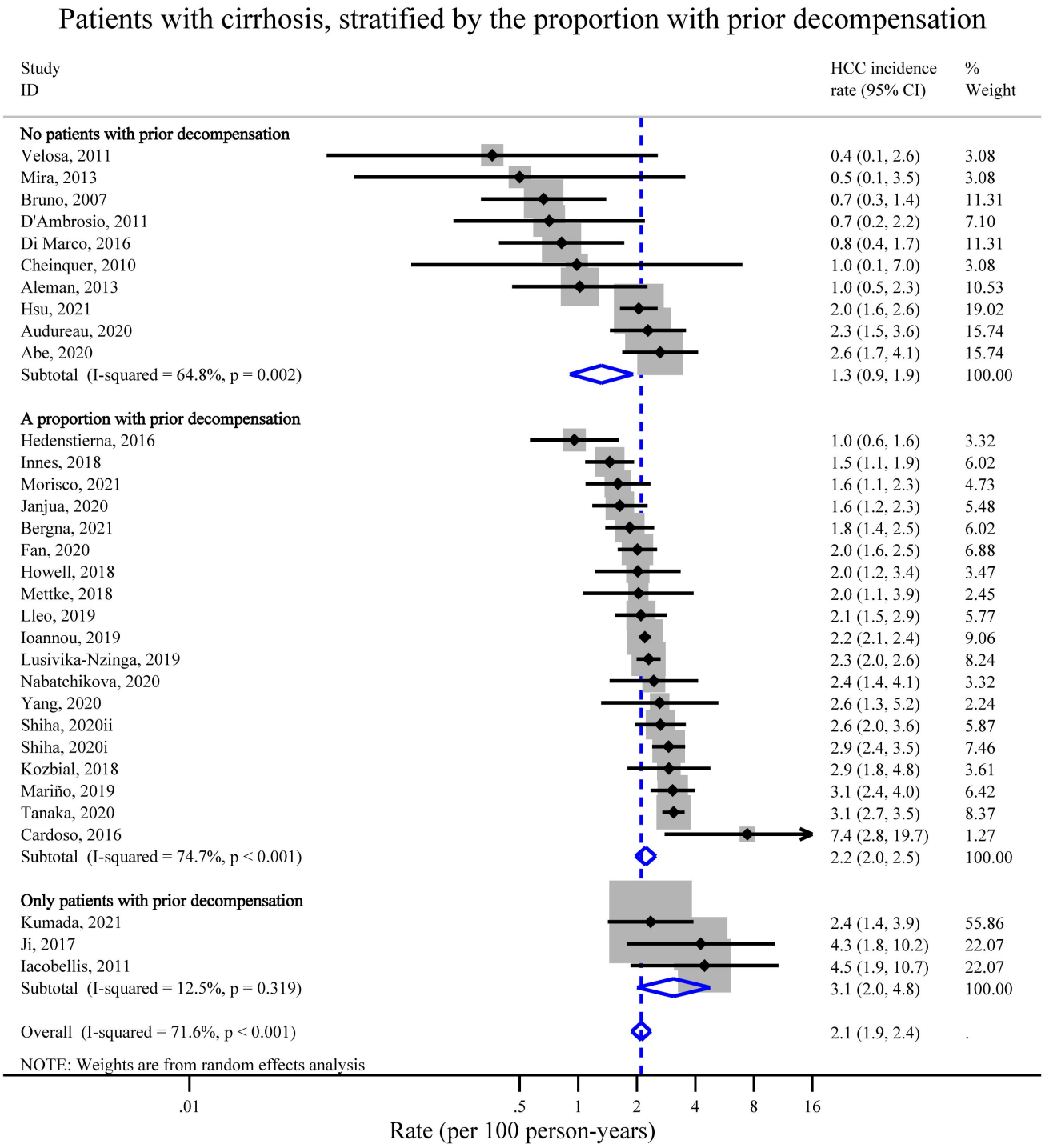

FIGURE 4 Forest plots of studies, evaluating HCC incidence rates after HCV cure among patients with cirrhosis, stratified by the proportion of patients with prior decompensation

but there appears to be a decreasing incidence over time, lowest in patients with compensated cirrhosis and younger age. In patients with F3 fibrosis and HCV cure, the HCC incidence is substantially lower and is below recommended thresholds for universal HCC screening. A more precise identification of patients at risk of HCC after HCV cure would clearly have significant cost-effectiveness and resource use implications. Our results should encourage the development of validated predictive models that better identify at-risk individuals, especially among patients with F3 fibrosis. Our results should also encourage cooperation to conduct a large multicenter cohort study assessing HCC risk over time after HCV cure.

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CONFLICT OF INTEREST

Dr. Dore received grants from Gilead, AbbVie, and Merck. Dr. Danta is on the speakers' bureau for and received grants from AbbVie. He is on the speakers' bureau for Gilead and Merck.

AUTHOR CONTRIBUTIONS

Ian Lockart, Behzad Hajarizadeh, Gregory J. Dore, and Mark Danta conceived the scope of the review. Screening, review, data extraction, and verification were done by Ian Lockart and Malcolm G. H. Yeo. Data analysis was done by Ian Lockart, which was reviewed by BH. Ian Lockart drafted the first iteration of manuscript. All authors made substantial contributions to the critical review, editing, and revision of the manuscript. All authors approved the final version of the manuscript.

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