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Estimation of fibrosis progression rates for chronic hepatitis C: a systematic review and meta-analysis update

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Abbreviations

HCV	hepatitis C virus
CHC	chronic Hepatitis C
FPR	fibrosis progression rate
BMI	body mass index
HBV	hepatitis B virus
HIV	human immunodeficiency virus
MMLE	markov maximum likelihood estimation
ALT	alanine aminotransferase
RNA	ribonucleic acid
CI	confidence interval
IDU	injection drug user
RR	relative risk
scFPR	stage-constant fibrosis progression rate

Abstract

Objectives: Mathematical models are increasingly important in planning for the upcoming chronic hepatitis C (CHC) elimination efforts. Such models require reliable natural history inputs to make accurate predictions on health and economic outcomes. Yet, HCV disease progression is known to vary widely in the literature and published inputs are currently outdated. The objectives of this study were to obtain updated estimates of fibrosis progression rates (FPRs) in treatment-naïve CHC patients and to explore sources of heterogeneity.

Design: A systematic review was conducted using Ovid-MEDLINE, Ovid-EMBASE, and PubMed databases (January 1990 – January 2018) to identify observational studies of hepatic fibrosis in treatment-naïve CHC patients.

Outcomes: Stage-constant FPRs were estimated for each study given the reported fibrosis scores and duration of infection. Stage-specific FPRs (i.e., F0→F1; F1→F2; F2→F3; F3→F4) were estimated using Markov Maximum Likelihood estimation. Estimates were pooled using random-effects meta-analysis and heterogeneity was evaluated by stratification and random-effects meta-regression.

Results: The review identified 111 studies involving 131 groups of patients (N=42,693). The pooled stage-constant FPR was 0.094 (95%CI, 0.088-0.100), stage-specific FPRs were F0→F1: 0.107 (95%CI, 0.097-0.118); F1→F2: 0.082 (95%CI, 0.074-0.091); F2→F3: 0.117 (95%CI, 0.107-0.129); F3→F4: 0.116 (95%CI, 0.104-0.131). Stratified analysis revealed substantial variation in progression by study population. Meta-regression indicated associations between progression and infection age, duration, source, viral genotype and study population. Findings indicate that FPRs display substantial heterogeneity across study populations and pooled values from more homogenous subpopulations should be considered when estimating prognosis.

Conclusions: This large meta-analysis presents updated prognostic estimates for CHC derived from newer studies using better diagnostic methods and improves estimates for important patient populations in terms of clinical policy (e.g., injection drug users, non-clinical populations, liver clinic patients) and should be a valuable resource for patients, clinicians and clinical policy makers.

Strengths and limitations of this study

- Our updated meta-analysis is now the largest review of HCV prognosis including English and non-English language observational studies.
- We use Markov maximum likelihood estimation method, which does not rely on the assumption of a linear disease progression to obtain detailed stage-specific estimates of fibrosis progression.
- Further, we restrict our meta-analysis to newer studies using better diagnostic methods compared to earlier reviews.
- Our analysis presents more precise prognostic estimates for important CHC subpopulations in terms of clinical policy (i.e., injection drug users, blood transfusion cohorts, liver clinic patients and non-clinical populations).
- Finally, we extensively explore study, clinical and viral sources of heterogeneity using stratification and through meta-regression analyses.

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Introduction

An estimated ~3% of the world's population is infected with the Hepatitis C virus (HCV) [1]. Chronic HCV (CHC) eventually leads to fibrosis, cirrhosis, advanced liver disease, and death [1–3]. The level of CHC-related hepatic fibrosis is typically detected through histology using the METAVIR scoring system with scores ranging from F0 indicating no fibrosis to F4 indicating cirrhosis. Published estimates of CHC prognosis has shown large variability in the rate of fibrosis progression across these stages [4–7].

Fortunately, HCV treatment has been revolutionized by highly effective therapies making elimination a plausible objective. Recently, the World Health Organization (WHO) launched a global strategy to this end, targeting a 90% reduction in new infections, a 65% reduction in liver-related death, a diagnosis rate of 90% and a treatment rate of 80% by 2030. This will necessitate radical expansions in prevention, screening and linkage to care [8].

However, a key challenge to the development of national elimination strategies has been the lack of reliable estimates of local disease burden, HCV prevalence and the prevalence of the undiagnosed population [8]. Currently, the only way to estimate such unknown parameters involves mathematical modeling. For this reason, WHO has been assisting countries through expert consultation and modelling initiatives [8]. Mathematical models are also increasingly important for estimating the health and economic consequences of scaling-up screening and treatment programs. However, these models require reliable natural history inputs to make accurate predictions [9,10]. Yet, HCV disease progression is known to vary widely in the literature and published natural history inputs are currently outdated [4–7].

In general, the variability in HCV disease progression has been attributed to differences in the study population (e.g., liver clinic, blood donors, injection drug users); differences due to study setting (i.e., clinical vs. non-clinical); differences among study subjects with respect to clinical risk factors for disease progression [11–13]; as well as to variation in the methods used for calculating fibrosis progression rates (FPRs) [14].

The established clinical risk factors for rapid progression of hepatic fibrosis include older age, male gender, excessive alcohol use, high body mass index (BMI), and HBV or HIV coinfection [11–13].

However, more recent studies have indicated race/ethnicity and viral genotype as possible risk factors as well [15–19]. Studies have also suggested that patients identified in clinical settings display a more rapid progression compared to those identified in non-clinical settings, for example by screening programs [4].

In terms of methodological variability, studies generally estimate progression using two methods: a direct method involving serial biopsies, and an indirect method involving a single biopsy and the estimated duration of infection [14]. Multiple biopsies are less common and often involve patients who need to be monitored closely for rapid progression; while, the more common indirect method assumes a constant progression rate from the time of infection despite evidence indicating variability between stages [4,20,21].

To account for stage-specific variation in progression, Yi *et al* [21] have proposed the Markov Maximum Likelihood Estimation (MMLE) method, which can estimate accurate stage-specific FPRs from observational studies where only a single biopsy and the estimated duration of infection are available. This has improved the external validity and accuracy of stage-specific progression estimates by allowing much larger numbers of single biopsy studies to inform HCV prognosis [21].

A previous systematic review from our group has estimated FPRs using this method [4]. This study has been widely-used in pharmacoeconomic evaluations. However, since its publication, a decade ago, new prognostic studies have become available, highlighting additional sources of variability (i.e., viral genotype, race/ethnicity) that merit further investigation [15–18,22,23].

Given the availability of new research and the importance of natural history estimates particularly for informing forthcoming elimination policies, the objectives of this study were: (1) to refine progression estimates through an updated systematic review of observational studies examining hepatic fibrosis in treatment naïve HCV-infected individuals and (2) to further explore additional sources of heterogeneity.

Materials and methods

Data sources

A systematic literature search was conducted using Ovid MEDLINE, Ovid EMBASE, and PubMed databases without language restriction by an experienced medical librarian (JB) [original: January 1990-

August 2007; update: January 2007-January 2018]. Additionally, the search was supplemented by citation searches and by reviewing references of relevant studies. Search strings for each database are provided in **Supplemental Methods.**

Study selection

Records were imported to EndNote X7.7.1 (Thomson Reuters, New York City, NY, USA). After duplicate removal, potentially relevant studies were screened against eligibility criteria by two independent reviewers. Disagreements were resolved through discussion.

Studies were included if they satisfied the following criteria: (1) CHC defined as the presence of anti-HCV antibody detected by second or third generation enzyme-linked immunosorbent assay and at least one of the following: HCV RNA detected by polymerase chain reaction, recombinant immunoblot assay, elevated alanine aminotransferase (ALT), or liver biopsy; (2) full-length peer-reviewed original observational study; and (3) no HCV treatment prior to biopsy. Studies involving fewer than 20 cases, post-liver transplant patients and those where FPRs could not be calculated were excluded. Multiple reports from the same study were identified by comparing author, year, and sample size. The report with the most complete information was preferred, if equivalent, then the most recent publication was included.

Data extraction

Study, host, viral and liver-disease related information were extracted in duplicate by two independent reviewers using piloted forms. For non-English studies, native speakers were contacted for help with full-text review and data extraction processes. A complete list of abstracted data items and all abstracted data are provided in the **Supplement**.

Age at HCV acquisition, for studies that did not report this information, was imputed by taking the difference between age at assessment and the estimated duration of infection. For some studies that report composite fibrosis stages (e.g., F0/F1), data were distributed 50:50 across F0 and F1. Stage distribution was not performed when more than two stages were reported collectively (e.g., F0/F1/F2). Definitions used by reviewers and criteria used to convert histological and non-invasive scores to the METAVIR system are provided in **S1 and S2 Tables** respectively.

Study quality

To improve accuracy and reduce relevant areas of bias, the updated meta-analysis was restricted to newer studies where all participants had confirmatory RNA testing for CHC. Further, studies were stratified by two independent reviewers by the mode of infection, which can influence the estimation of the duration of infection, as well as by study design, setting and population based on criteria described in **Table S2**. Finally, other clinical factors such as excess alcohol use and HIV or HBV coinfection among study subjects were adjusted for using meta-regression analyses.

Estimation of fibrosis progression rates

Two methods were used to estimate the annual FPRs for each included study: (1) The stage-constant FPR was estimated by dividing the total number of transitions in METAVIR units by the person-years of HCV infection; (2) The stage-specific FPRs (i.e., F0→1, F1→2, F2→3 and F3→F4) were estimated using the MMLE method [21].

Data synthesis

Identified groups were stratified by methodological and clinical subgroups. Estimates were pooled by random-effects meta-analyses. Time-to-cirrhosis was determined using the pooled stage-specific progression rates (α_s) [4,21]:

$$Time - to - Cirrhosis = \left(\frac{1}{\alpha_{01}} + \frac{1}{\alpha_{12}} + \frac{1}{\alpha_{23}} + \frac{1}{\alpha_{34}}\right)$$

Finally, the pooled FPRs and their 95% confidence intervals (CI) were used to estimate the mean cumulative probability of cirrhosis up to 40 years after HCV exposure for clinically important subpopulations.

Heterogeneity

For all estimates, publication bias, small study effects and heterogeneity were assessed by visual inspection of funnel plots of the natural log of FPRs against inverse variance. A statistical test for funnel plot was not performed due to presence of significant heterogeneity (**S1 Fig)** [24,25]. Heterogeneity was quantified using the I^2 statistic, with values of 25% and 75% indicating low and high heterogeneity [26].

Previously identified sources of heterogeneity (e.g., study-related, methodological, clinical and viral) were explored through stratification and random-effects meta-regression analyses using a linear mixed model – maximum likelihood method weighted by a multiplicative variance adjustment factor [4,11–13,17]. Missing values were imputed using the mean values. The natural log of FPRs were used as the dependent variable.

Statistical analysis

Statistical analysis was conducted using SAS (SAS Inc, Cary, NC, USA) and PROC MIXED and PROC MIXED ML procedures were used for all meta-analyses and meta-regression analyses. The plots were generated using RStudio v1.1.383 (RStudio, Boston, MA, USA). A two-sided significance level of 0.05 was used to indicate significance for hypothesis tests.

Results

Study selection

The current study is an update of a previous review covering the period from January 1990 to August 2007 [4]. The updated literature search (January 2007- January 2018) identified a total 10,440 records **(Fig 1)**. Following duplicate removal, 7,193 abstracts were screened, and 1,304 records were included for full-text review. Overall, the update identified 45 new studies reporting on 60 new patient groups (24,689 HCV infected subjects) resulting in total of 140 studies and 171 groups of patients (57,810 subjects) in combination with the earlier review. Group-level summary of study and participant characteristics are provided in **S3 and S4 Tables** respectively.

However, the updated meta-analysis was restricted to newer studies where all participants had HCV RNA testing. After elimination of 40 study groups where RNA status was either missing or unclear, the updated meta-analysis included 111 studies reporting on 131 groups of patients (42,693 subjects and 723,058 person-years of follow-up time).

Study characteristics

The study characteristics of the 131 groups are summarized in **Table 1.** A majority, 84% (N=110), of the included groups were assessed in a clinical setting (vs. non-clinical). Compared to the original review, the update identified relatively more patients evaluated in a non-clinical setting [12% (N=3,068) of original vs. 31% (N=5,392) of new subjects]. In terms of study design, a majority, 68% (N=88) used a cross-sectional/retrospective vs. a retrospective-prospective study design.

Regarding the patient populations, liver clinic patients were the most frequently studied group (69%). In total, there were 91 groups of liver clinic patients; 10 of injection drug users (IDUs); 6 of dialysis patients; 5 of females, 4 community, renal transplant recipients and infectious diseases patients; 3 of blood donor groups; and 2 of pediatric and post-transfusion groups (**Table 1**). Furthermore, the update identified a total of 10 evaluations of genotype-1, 3 of genotype-3 and 1 each of genotypes 2 and 4 infected groups.

Clinical characteristics of study subjects

The clinical characteristics of subjects are summarized in **S5 Table**. The majority of the subjects were male (62%) and white (69%). The mean age at assessment of liver fibrosis was 44 years, the mean age at infection was 26 years and the mean duration of infection of 18 years. The average prevalence of excess alcohol use was 20%. Injection drug use accounted for 43% and blood transfusion for 26% of infections. Cirrhosis was present in 12%. The majority, of the subjects (76%) had an elevated ALT. The mean ALT of all subjects was 88IU/L. In terms of viral genotype, the average prevalence of genotype-1 was 56%, genotype-3 was 18%. On average, 2% of subjects were coinfected with HIV and 0.4% with HBV.

Overall fibrosis progression rates

The pooled stage-constant FPR was 0.094 (95%CI, 0.088-0.100) METAVIR units per year (**Table 2**). The stage-specific FPR estimates were generally lower for transitioning between F0→F1 (0.107; 95%CI, 0.097-0.118) and F1→F2 (0.082; 95%CI, 0.074-0.091); relative to F2→F3 (0.117; 95%CI, 0.107-0.129) and F3→F4 (0.116; 95%CI, 0.104-0.131). Overall, the estimated time-to-cirrhosis was 39 years. The I^2-

statistic indicated a high level of heterogeneity which were relatively more pronounced at earlier stages. The pooled FPRs stratified by study update are provided in **S6 Table**.

Stratification by study setting and design

Time-to-cirrhosis estimates indicated a faster progression to cirrhosis in groups evaluated in a clinical vs. non-clinical setting (37 vs. 47 years) (**Table 2**). In terms of study design, there was only a small difference in progression among cross-sectional/retrospective vs. retrospective-prospective design (38 vs. 41 years), which was lost following adjustment for covariates (**S7 Table**). The cumulative probability of cirrhosis by study setting is presented in **Fig 2**.

Stratification by study population

Time-to-cirrhosis estimates indicated a relatively slower progression to cirrhosis for the female (74 years), blood donor (63 years), pediatric (45 years), and post transfusion cohorts (44 years) and a faster progression for infectious diseases (19 years), renal transplant (24 years), dialysis (35 years), community (35 years) and IDU (37 years) populations relative to liver clinic populations (40 years) (**Table 2**).

In general, simple stratification by study population was able to explain heterogeneity in estimates primarily for the later stages of disease. However, a high level of heterogeneity persisted for liver clinic, IDU and community groups. The unadjusted cumulative probability of cirrhosis for different study populations are displayed in **Fig 2**.

Based on time-to-cirrhosis estimates derived from covariate-adjusted FPRs, female (52 years), blood donor (55 years) and post-transfusion (44 years) groups maintained a relatively slower progression, while pediatric groups (36 years) displayed a slightly faster progression relative to liver clinic populations (38 years) (**S7 Table)**. Infectious diseases (34 years) and community (33 years) groups maintained a relatively faster progression following adjustments, while the covariate-adjusted progression was somewhat comparatively slower for dialysis patients (47 years), renal transplant (39 years) and IDUs (40 years).

Stratification by publication year

Based on unadjusted time-to-cirrhosis estimates, earlier studies (< year 2000) indicated a slower progression to cirrhosis (49 years) vs. studies published after 2000 (**Table 2)**. This was also apparent following covariate adjustment (**S7 Table**).

Stratification by age and duration of infection

In terms of age, groups with a younger mean age at assessment (<40 years) displayed a faster progression to cirrhosis (33 years) vs. an older age (≥40) (40 years) (**Table 2**). While groups with an older age at infection (≥ 30 years) displayed a more rapid progression (20-28 years) relative to a younger age (< 30 years) (42-45 years). Fibrosis also progressed faster (17 years) in groups with a shorter duration of infection (< 10 years).

Stratification by viral genotype

Regarding viral genotype, groups infected with viral genotype-1 displayed a much slower progression to cirrhosis vs. genotype-3 (59 vs. 30 years) (**Table 2**). Slower progression for genotype-1 vs. genotype-3 groups remained following covariate adjustments (43 vs. 34 years) (**S7 Table)**. In the stratified analysis, genoytpe-3 groups exhibited considerably less heterogeneity vs. genotype-1. The unadjusted cumulative probability of cirrhosis for genotypes 1 and 3 are displayed in **Fig 2**.

Univariate analysis

In the univariate analyses, most clinical covariates displayed an association with at least one progression estimate except for HIV coinfection, male sex, white and Asian race (**S8 Table**). For more advanced stages of disease, genotype-1 was associated with a slower progression to advanced fibrosis (F2→F3; RR=0.53) and to cirrhosis (F3→F4; RR=0.39); while, genotype-3 was associated with faster progression to cirrhosis (RR=2.62). Additionally, injection drug related infections displayed faster (RR=1.65) and black race slower progression (RR=0.47) to cirrhosis.

Regarding study-related factors, studies conducted in a non-clinical setting (vs. clinical) indicated a slower progression in the earlier stages of disease (RR=0.68-0.75). In terms of study population, relative to liver clinic patients, IDUs (RR=1.72) and infectious diseases groups (RR=2.26), displayed a faster and females

(RR=0.46) displayed a slower progression to cirrhosis. For earlier stages, dialysis, renal transplant and infectious diseases populations all exhibited a faster (RR=2.12-2.54) and females again displayed a slower progression (RR=0.45). Many covariates (e.g., infectious diseases, females, genotype 3) were also associated with the overall progression (scFPR).

Multivariable analysis

After adjusting for multiple covariates (**Table 3**), the duration of infection remained independently associated with slower progression for all FPRs (RR=0.94-0.97). Age at infection was also independently associated with faster progression between F1→F2 (RR=1.03) and with overall progression (scFPR; RR=1.01). Similarly, blood transfusion-related infection displayed faster progression from F0→F1 (RR=2.37) and in overall progression (scFPR; RR=1.63). Regarding viral genotype, following adjustment for covariates, genotype-1 was significantly associated with a slower progression between F2→F3 (RR=0.58) and faster progression from F0→F1 (RR=1.61). No significant association was observed for viral genotype-3 or for ethnicity. In terms of study-related factors, only dialysis populations maintained a significant association after covariate-adjustment, exhibiting a slower progression vs. liver clinic patients, at early stages (F1→F2; RR=0.58). Based on the adjusted-R^2, covariates explained ~38-56% of the heterogeneity in the stage-specific FPR estimates and 87% in the stage-constant estimate.

Discussion

Our large systematic review of HCV natural history presents updated and refined estimates of CHC-related hepatic fibrosis progression in treatment naïve patients. Overall, the updated estimates were generally consistent with previous studies and indicated an average time-to-cirrhosis of ~39 years [4,27,28]. However, the current study found a slightly slower progression compared to our previous analysis, especially at the earliest stage of fibrosis [4].

The current update improves upon our previous analysis by focusing on more recent studies where CHC was confirmed by better diagnostic methods and by incorporating substantially more subjects identified in a non-clinical setting (8,460 vs. 3,068) and more IDU populations (5,132 vs. 670) thereby providing more precise estimates of progression for these important subpopulations. Further, we identified study

population as an important source of heterogeneity indicating that population-specific estimates should be considered when estimating prognosis.

In our updated analysis we also further explored the effects of viral genotype and race/ethnicity on prognosis. Univariate analyses identified genotype-3 as a predictor of faster and genotype-1 a predictor of slower progression from advanced fibrosis to cirrhosis. Similarly, a previous meta-analysis of stage-constant FPR also found a faster progression for genotype-3 vs non-3 groups [17]. Due to the small number of studies a meta-regression could not be used to explore confounders in that study. In our large meta-regression, genotype-1 displayed a faster progression at the earliest but a slower progression at more advanced stages of fibrosis. Similarly, univariate analysis also indicated a slower progression from significant fibrosis to cirrhosis for black race and female populations in agreement with previous studies; [19,23,29] although these relationships were lost upon covariate adjustment.

Our study is limited in several ways. We excluded reports where the data on infection duration were not available. Thus, the results may not be generalizable to individuals with an unknown source of infection. Moreover, estimates based on self-report such as, the duration of infection, alcohol and drug use, may suffer from recall bias. Studies in IDUs suggest that there may exist a median lag of ~3 years between the first year of drug use and HCV-infection [16,30]. Therefore, the accuracy of the estimates of infection duration may vary by the mode of infection [31], resulting in a possible underestimation of FPRs for IDUs. Additionally, alcohol use tends to be inconsistently reported. Finally, aggregated analyses may suffer from ecological fallacy [32]. It is also important to note that although newer non-invasive methods are replacing biopsy, non-invasive prognosis currently remains limited making biopsy-based stage-specific estimates the most suitable method for representing the natural history of HCV at the current time [33].

Finally, our analyses identified substantial heterogeneity, especially among earlier vs. later stages of fibrosis. This is not surprising as published estimates are known to vary extensively. While we have explained some of this variation, it is possible that some heterogeneity is also related to sampling variability associated with biopsies, though, non-invasive estimates also demonstrate considerable variability [33]. Other sources of variation may include obesity, steatosis, insulin resistance or genetic factors that can moderate fibrogenesis, which remain largely unreported in the literature [34–38].

Furthermore, I^2-statistic, which measures the extent of variation due to heterogeneity vs. sampling error may be inflated when study sizes are large or sampling error is low as in our case [39].

Our study also has significant strengths: (1) it is the largest meta-analysis of HCV prognosis including English and non-English language studies; (2) it uses the MMLE method to obtain detailed stage-specific estimates of HCV prognosis in treatment naïve patients, a method that does not rely on the assumption of linear disease progression; (3) compared to our original study, the current update improves the precision of prognostic estimates for important patient groups in terms of clinical-policy (i.e., asymptomatic patients identified in non-clinical settings through screening efforts, injection drug users, blood transfusion populations, liver clinic patients); (4) our update was also restricted to more recent studies where CHC is identified using better diagnostic tests; (5) further, the large numbers of included studies has allowed for us to explain ~38-87% of the apparent heterogeneity in progression; and finally, (6) we present natural history data that can be easily applied to mathematical models for estimating HCV prevalence, disease burden, resource utilization, budget impact and cost-effectiveness, all of which will be necessary for planning appropriate elimination programs in the near future. Furthermore, given the level of heterogeneity identified across studies, our updated analysis suggests that pooled progression estimates from more homogenous subpopulations should be considered when estimating prognosis in policy models.

In Conclusion, the accurate estimation of HCV disease progression remains important in the era of HCV elimination particularly due to existing policy question around elimination strategies, which necessitate modeling-based methods to help inform policy. The current study is now the largest and most detailed review of HCV prognosis, which presents more precise prognostic estimates for important subpopulations in terms of clinical policy and should be a valuable resource for clinicians, patients and particularly clinical policy makers.

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Table 1: Summary of subgroups included in the meta-analysis.

	Updated Review (1990-2018)		Original Review (1990-2007)		New Groups (2007-2018)	
	N	SS	N	SS	N	SS
All groups	131	42,693	81	25,492	50	17,201
Study setting						
Clinical	110	34,233	70	22,424	40	11,809
Non-clinical	21	8,460	11	3,068	10	5,392
Study design						
Cross-sectional/Retrospective	88	29,088	72	22,921	16	6,167
Retrospective-Prospective	43	13,605	9	2,571	34	11,034
Study population						
Females	5	1,420	4	1,400	1	20
Blood donors	3	408	2	223	1	185
Pediatric patients	2	223	0	.	2	223
Post transfusion	2	509	1	469	1	40
Liver clinic	91	32,524	61	21,338	30	11,186
Injection drug users	10	5,132	4	670	6	4,462
Community	4	1,451	3	1,044	1	407
Dialysis patients	6	408	3	191	3	217
Renal transplant	4	179	3	157	1	22
Infectious diseases	4	439	0	.	4	439
Publication year						
<2000	4	629	4	629	0	0
2000 to <2005	56	16,460	54	16,309	2	151
2005 to<2010	37	12,041	23	8,554	14	3,487
≥2010	34	13,563	0	.	34	13,563
Age at assessment						
Age<40	23	5,540	13	2,166	10	3,374
Age≥ 40	108	37,153	68	23,326	40	13,827
Estimated age at Infection						
<20 years	11	2,318	4	662	7	1,656
30 to <40 years	95	35,926	64	21,576	31	14,350
20 to <30 years	19	3,864	13	3,254	6	610
≥40 years	6	585	0	.	6	585
Estimated duration of infection						
<10 years	8	834	2	212	6	622
10 to <20 years	71	21,949	50	13,800	21	8,149
≥ 20 years	52	19,910	29	11,480	23	8,430
HCV genotype						
Genotype 1	10	3,000	5	1,854	5	1,146
Genotype 2	1	90	0	.	1	90
Genotype 3	3	1,426	0	.	3	1,426
Genotype 4	1	117	0	.	1	117

Table 1. Summary of subgroups included in the meta-analysis. The meta-analysis was restricted to 131 study groups (81 from the original review and 50 new groups) where CHC was confirmed by HCV RNA testing in all subjects. Abbreviations: N: number of groups included in the meta-analysis; SS: total sample size in each group.; CHC: chronic hepatitis C.

Table 2: Random-effects meta-analysis of hepatic fibrosis progression rates stratified by CHC subgroups.

		F0 → F1				F1 → F2				F2 → F3				F3 → F4				scFPR				TTC*
	N	Mean	95% CI		I^2	Mean	95% CI		I^2	Mean	95% CI		I^2	Mean	95% CI		I^2	Mean	95% CI		I^2	(yrs)
All groups	131	0.107	0.097	0.118	98%	0.082	0.074	0.091	97%	0.117	0.107	0.129	94%	0.116	0.104	0.131	89%	0.094	0.088	0.100	85%	39
Study setting																						
Clinical	110	0.114	0.103	0.126	98%	0.086	0.077	0.096	98%	0.118	0.106	0.132	93%	0.119	0.105	0.133	89%	0.097	0.091	0.103	82%	37
Non-clinical	21	0.077	0.058	0.104	98%	0.065	0.053	0.081	96%	0.111	0.088	0.139	91%	0.101	0.068	0.150	94%	0.076	0.036	0.150	90%	47
Study design																						
Cross-sectional/Retrospective	88	0.114	0.101	0.129	98%	0.082	0.072	0.094	98%	0.119	0.107	0.133	93%	0.120	0.105	0.136	87%	0.097	0.090	0.104	84%	38
Retrospective-Prospective	43	0.093	0.079	0.110	98%	0.082	0.071	0.094	96%	0.114	0.094	0.138	95%	0.110	0.087	0.140	92%	0.088	0.078	0.098	85%	41
Study population**																						
Females	5	0.048	0.026	0.088	97%	0.051	0.043	0.061	27%*	0.071	0.049	0.103	47%*	0.051	0.025	0.106	46%*	0.053	0.036	0.078	53%*	74
Blood donors	3	0.067	0.017	0.264	96%	0.051	0.020	0.128	82%	0.094	0.018	0.487	83%	0.057	0.009	0.340	55%*	0.065	0.028	0.152	42%*	63
Pediatric patients	2	0.201	0.074	0.550	0%*	0.087	0.015	0.506	56%*	0.096	0.107	0.125	87%	0.055	0.028	0.585	0%*	0.133	0.009	1.984	0%*	45
Post transfusion	2	0.065	0.034	0.125	0%*	0.079	0.002	2.593	80%	0.114	0.038	0.341	0%*	0.134	0.033	0.545	0%*	0.081	0.028	0.230	0%*	44
Liver clinic	91	0.106	0.095	0.118	98%	0.082	0.072	0.092	98%	0.111	0.100	0.123	94%	0.112	0.100	0.127	88%	0.092	0.087	0.099	65%*	40
Injection drug users	10	0.109	0.071	0.168	99%	0.071	0.052	0.096	96%	0.121	0.086	0.170	92%	0.194	0.135	0.278	84%	0.094	0.072	0.123	88%	37
Community	4	0.134	0.082	0.218	94%	0.088	0.047	0.164	96%	0.111	0.074	0.167	83%	0.133	0.065	0.271	88%	0.104	0.086	0.125	22%*	35
Dialysis patients	6	0.121	0.060	0.244	95%	0.074	0.047	0.116	69%*	0.250	0.114	0.547	71%*	0.114	0.069	0.189	0%*	0.100	0.068	0.148	20%*	35
Renal transplant	4	0.225	0.094	0.540	89%	0.173	0.070	0.426	84%	0.190	0.074	0.490	64%*	0.117	0.041	0.331	0%*	0.190	0.076	0.475	60%*	24
Infectious diseases	4	0.144	0.084	0.247	89%	0.211	0.145	0.307	48%*	0.273	0.096	0.774	89%	0.256	0.047	1.379	92%	0.171	0.097	0.302	68%*	19
Publication year																						
<2000	4	0.068	0.030	0.154	96%	0.049	0.024	0.103	84%	0.124	0.058	0.264	48%*	0.172	0.058	0.513	48%*	0.068	0.033	0.143	61%*	49
2000 to <2005	56	0.119	0.101	0.140	98%	0.076	0.064	0.091	98%	0.116	0.101	0.132	91%	0.122	0.106	0.140	79%	0.095	0.087	0.105	83%	38
2005 to <2010	37	0.096	0.081	0.113	98%	0.085	0.074	0.097	94%	0.100	0.085	0.117	92%	0.092	0.074	0.114	89%	0.087	0.078	0.097	82%	43
≥2010	34	0.106	0.088	0.129	98%	0.096	0.080	0.116	97%	0.143	0.113	0.181	96%	0.137	0.102	0.184	95%	0.102	0.090	0.116	86%	34
Age at assessment																						
Age<40	23	0.128	0.096	0.172	98%	0.088	0.069	0.112	96%	0.142	0.114	0.177	86%	0.141	0.105	0.189	80%	0.113	0.095	0.134	78%	33
Age≥40	108	0.103	0.093	0.114	98%	0.081	0.072	0.091	98%	0.113	0.102	0.125	94%	0.113	0.099	0.127	90%	0.091	0.085	0.097	84%	40
Estimated age at infection																						
<20 years	11	0.097	0.060	0.155	98%	0.061	0.044	0.085	94%	0.118	0.082	0.170	84%	0.108	0.065	0.179	77%	0.083	0.063	0.110	75%*	45
20 to <30 years	95	0.100	0.090	0.112	98%	0.075	0.068	0.084	98%	0.104	0.095	0.115	93%	0.109	0.096	0.124	90%	0.088	0.083	0.094	83%	42
30 to <40 years	19	0.128	0.100	0.164	97%	0.127	0.099	0.163	95%	0.177	0.136	0.229	91%	0.146	0.115	0.185	75%*	0.124	0.104	0.146	79%	28
≥40 years	6	0.200	0.143	0.278	82%	0.147	0.090	0.239	83%	0.234	0.094	0.584	91%	0.246	0.098	0.619	78%	0.160	0.108	0.237	52%*	20
Estimated duration of infection																						
<10 years	8	0.218	0.162	0.295	90%	0.175	0.118	0.261	87%	0.290	0.136	0.619	89%	0.314	0.157	0.629	62%*	0.209	0.168	0.258	0%*	17
10 to <20 years	71	0.128	0.113	0.145	98%	0.081	0.070	0.094	98%	0.130	0.116	0.145	89%	0.133	0.117	0.152	82%	0.106	0.099	0.114	75%*	35
≥20 years	52	0.075	0.067	0.084	97%	0.075	0.067	0.084	95%	0.092	0.080	0.104	89%	0.090	0.076	0.106	91%	0.076	0.071	0.081	70%*	49
HCV genotype																						
Genotype-1	10	0.072	0.049	0.108	98%	0.074	0.052	0.107	96%	0.072	0.061	0.083	58%*	0.056	0.029	0.107	92%	0.072	0.055	0.093	83%	59
Genotype non-1	6	0.096	0.065	0.142	93%	0.091	0.070	0.117	76%	0.102	0.069	0.149	79%	0.175	0.112	0.274	63%*	0.096	0.072	0.128	65%*	37
Genotype-3	3	0.134	0.084	0.213	77%	0.103	0.084	0.126	2%*	0.112	0.049	0.253	83%	0.247	0.165	0.370	0%*	0.119	0.080	0.175	36%*	30
Genotype non-3	15	0.079	0.060	0.103	98%	0.079	0.062	0.102	95%	0.076	0.067	0.087	66%*	0.073	0.043	0.122	93%	0.077	0.065	0.092	78%	52

Table 2. Annual fibrosis progression rates based on random-effects meta-analyses. The meta-analysis was restricted to 131 study groups where CHC was confirmed by HCV RNA testing in all subjects. Abbreviations: scFPR: stage-constant annual progression rate (assuming linear progression from stage F0 to F4); I^2: the proportion of variability in progression rates due to heterogeneity vs. sampling error; N: number of groups included in the meta-analysis; *TTC: time-to-cirrhosis (based on unadjusted stage-specific FPRs). *Study subgroups with low-to-moderate heterogeneity; **Study populations are ordered by progression from slowest to fastest based on TTC. Notes: The estimates are not adjusted for covariates and maybe confounded. Note: Genotype non-1 and non-3 groups are composed of 65% genotype-3 and 82% genotype-1 respectively.

Table 3: Random-effects meta-regression of covariates associated with hepatic fibrosis progression rates

Covariates	F0→F1*				F1→F2*				F2→F3*				F3→F4*				scFPR*			
	β	SE	P-value	RR	β	SE	P-value	RR	β	SE	P-value	RR	β	SE	P-value	RR	β	SE	P-value	RR
Intercept	-2.564	0.555	<.0001		-3.482	0.675	<.0001		-1.031	0.608	0.093		-1.400	0.766	0.071		-2.438	0.312	<.0001	
Study design																				
Cross-sectional/Retro (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
Retrospective-Prospective	-0.088	0.093	0.347	*0.92*	0.041	0.113	0.717	*1.04*	-0.001	0.100	0.991	*1.00*	0.036	0.126	0.773	*1.04*	0.011	0.050	0.834	*1.01*
Study population																				
Liver clinic (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
Females	-0.149	0.334	0.656	*0.86*	0.318	0.400	0.428	*1.37*	-0.073	0.349	0.834	*0.93*	-0.616	0.442	0.166	*0.54*	-0.046	0.170	0.790	*0.96*
Blood donors	-0.040	0.256	0.875	*0.96*	-0.318	0.314	0.313	*0.73*	-0.276	0.289	0.342	*0.76*	-0.707	0.395	0.076	*0.49*	-0.175	0.166	0.296	*0.84*
Pediatric patients	0.361	0.475	0.449	*1.43*	0.831	0.567	0.145	*2.30*	-0.054	0.521	0.918	*0.95*	-0.199	0.750	0.791	*0.82*	0.479	0.307	0.121	*1.61*
Post-transfusion	-0.343	0.407	0.402	*0.71*	-0.206	0.493	0.676	*0.81*	-0.143	0.466	0.760	*0.87*	-0.853	0.651	0.192	*0.43*	-0.093	0.282	0.742	*0.91*
Injecting drug users	0.278	0.221	0.211	*1.32*	-0.310	0.268	0.251	*0.73*	0.120	0.243	0.621	*1.13*	0.499	0.293	0.091	*1.65*	0.070	0.115	0.543	*1.07*
Community	0.226	0.209	0.283	*1.25*	0.167	0.248	0.503	*1.18*	0.016	0.204	0.938	*1.02*	0.192	0.241	0.428	*1.21*	0.125	0.087	0.154	*1.13*
Dialysis patients	-0.121	0.203	0.551	*0.89*	-0.550	0.248	**0.028**	***0.58***	0.299	0.250	0.233	*1.35*	-0.103	0.307	0.738	*0.90*	-0.235	0.153	0.127	*0.79*
Renal transplant recipients	-0.012	0.236	0.961	*0.99*	0.262	0.285	0.359	*1.30*	0.064	0.274	0.815	*1.07*	-0.372	0.412	0.368	*0.69*	0.164	0.191	0.390	*1.18*
Infectious diseases	-0.261	0.241	0.282	*0.77*	0.304	0.294	0.304	*1.35*	0.264	0.257	0.305	*1.30*	0.211	0.314	0.502	*1.24*	-0.013	0.139	0.924	*0.99*
Publication year																				
<2000 (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
2000 to <2005	0.406	0.241	0.094	*1.50*	0.116	0.299	0.698	*1.12*	-0.010	0.295	0.973	*0.99*	-0.543	0.369	0.143	*0.58*	0.227	0.164	0.169	*1.25*
2005 to <2010	0.492	0.242	**0.044**	***1.64***	0.352	0.300	0.242	*1.42*	-0.009	0.297	0.975	*0.99*	-0.583	0.372	0.120	*0.56*	0.310	0.165	0.062	*1.36*
≥2010	0.404	0.246	0.103	*1.50*	0.356	0.306	0.246	*1.43*	0.227	0.301	0.451	*1.26*	-0.500	0.377	0.187	*0.61*	0.369	0.166	**0.028**	***1.45***
Gender – male†	0.592	0.437	0.178	*1.81*	0.704	0.520	0.179	*2.02*	-0.103	0.454	0.822	*0.90*	-0.157	0.564	0.781	*0.85*	0.289	0.217	0.186	*1.34*
Age at HCV infection (yrs.)	0.004	0.011	0.698	*1.00*	0.033	0.013	**0.012**	***1.03***	0.012	0.011	0.292	*1.01*	0.020	0.014	0.169	*1.02*	0.014	0.006	**0.014**	***1.01***
Duration of infection (yrs.)	-0.063	0.010	**<.0001**	***0.94***	-0.028	0.012	**0.022**	***0.97***	-0.048	0.010	**<.0001**	***0.95***	-0.043	0.013	**0.001**	***0.96***	-0.049	0.005	**<.0001**	***0.95***
Injecting drug use†	0.194	0.248	0.435	*1.21*	-0.114	0.298	0.701	*0.89*	-0.117	0.262	0.656	*0.89*	0.301	0.328	0.361	*1.35*	0.090	0.132	0.497	*1.09*
Blood transfusion†	0.862	0.298	**0.005**	***2.37***	0.260	0.355	0.466	*1.30*	0.219	0.302	0.469	*1.25*	0.464	0.369	0.211	*1.59*	0.486	0.145	**0.001**	***1.63***
Excess alcohol use†	-0.312	0.263	0.238	*0.73*	0.591	0.314	0.062	*1.81*	0.177	0.273	0.517	*1.19*	0.245	0.329	0.458	*1.28*	0.201	0.131	0.126	*1.22*
HIV positive†	0.075	0.839	0.929	*1.08*	0.532	1.009	0.599	*1.70*	-0.506	0.907	0.578	*0.60*	0.191	1.105	0.863	*1.21*	-0.312	0.429	0.469	*0.73*
Genotype-1†	0.473	0.221	**0.034**	***1.61***	-0.380	0.264	0.153	*0.68*	-0.539	0.224	**0.018**	***0.58***	-0.313	0.274	0.256	*0.73*	-0.051	0.108	0.637	*0.95*
Genotype-3†	0.226	0.277	0.416	*1.25*	0.036	0.331	0.914	*1.04*	-0.273	0.285	0.341	*0.76*	0.194	0.347	0.577	*1.21*	0.093	0.133	0.487	*1.10*
White†	0.160	0.197	0.420	*1.17*	-0.047	0.238	0.845	*0.95*	-0.325	0.208	0.120	*0.72*	0.032	0.256	0.900	*1.03*	-0.045	0.102	0.660	*0.96*
Black†	-0.302	0.273	0.272	*0.74*	0.332	0.330	0.317	*1.39*	-0.011	0.287	0.970	*0.99*	-0.609	0.356	0.089	*0.54*	-0.005	0.139	0.971	*0.99*
Asian†	0.086	0.354	0.808	*1.09*	0.268	0.431	0.534	*1.31*	0.003	0.404	0.994	*1.00*	0.933	0.534	0.083	*2.54*	0.061	0.242	0.800	*1.06*
I^2_{Res}		*96%*				*96%*				*86%*				*77%*				*39%*		
Adjusted R^2		*56%*				*38%*				*54%*				*53%*				*87%*		

Table 3. Linear mixed model-maximum likelihood method. *Log progression rates. †Proportion. Values in bold indicate statistical significance. Abbreviations: scFPR: stage-constant annual fibrosis progression rates (assuming linear progression from F0 to F4); β: coefficient; SE: standard error; HIV: human immunodeficiency virus; RNA: ribonucleic acid; ref: reference category; adjusted R^2: the proportion of heterogeneity explained by covariates in the model; I^2_{res}: the proportion of residual variability due to heterogeneity.

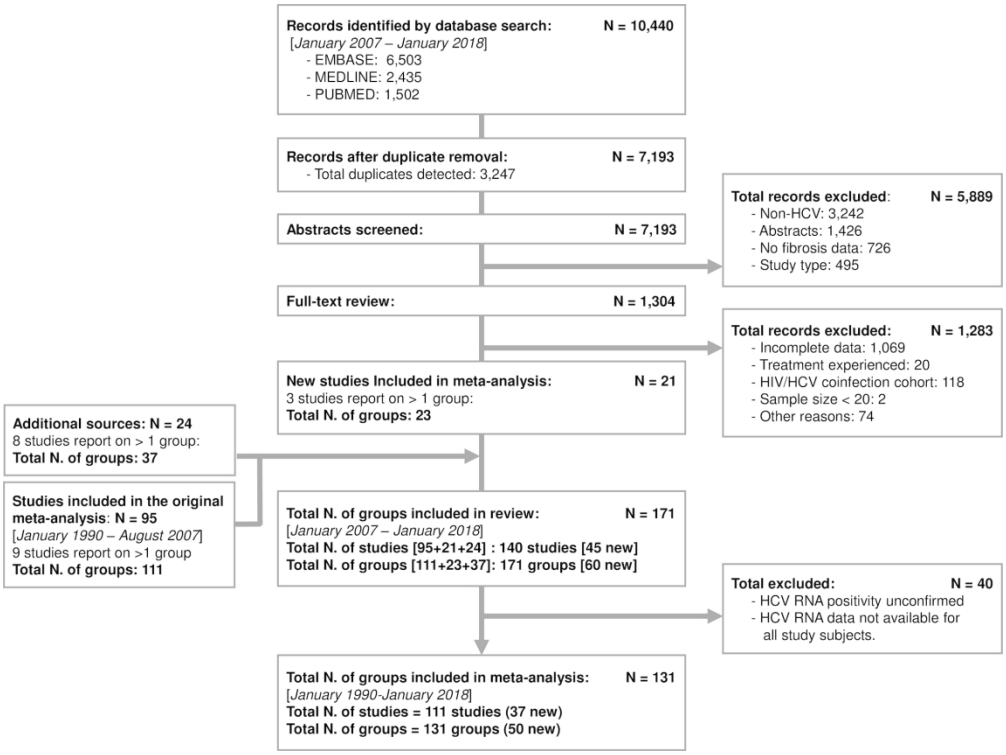
Figure legends

Fig 1. PRISMA flow diagram showing the study selection progress.

The literature search recovered a total of 5,718 citations. Following duplicate removal and supplementary citation searches, the review process identified a total of 45 new studies reporting on 60 groups of HCV-infected patients. Together with the 95 studies reporting on 111 groups identified by the original review, the current update identified a total of 140 studies of 171 HCV-infected groups of patients. Meta-analysis was restricted to 111 studies reporting on 131 study groups where CHC was confirmed by HCV RNA testing in all subjects.

Fig 2. Cumulative probability of cirrhosis for various patient populations.

Figure showing the cumulative probability of cirrhosis over years of HCV infection for (A) all study groups by estimation method; and groups stratified by (B) study setting; (C) viral genotype; and (D) study population using stage-specific progression rate estimates. Cumulative probabilities are projected using unadjusted estimates and maybe confounded. Note: high degree of heterogeneity is present within liver



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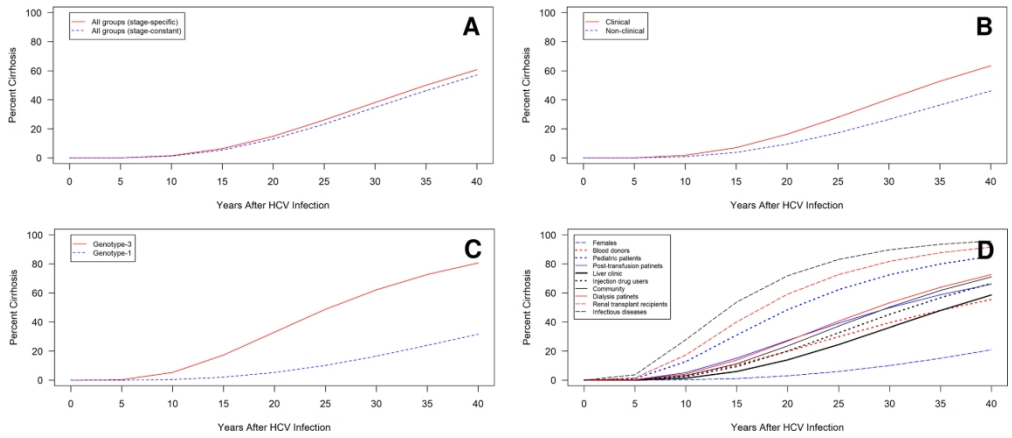

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190x80mm (300 x 300 DPI)

Supplementary Materials

List of Supplementary Materials:

1. S1 Figure: Funnel plots for hepatic fibrosis progression rates.
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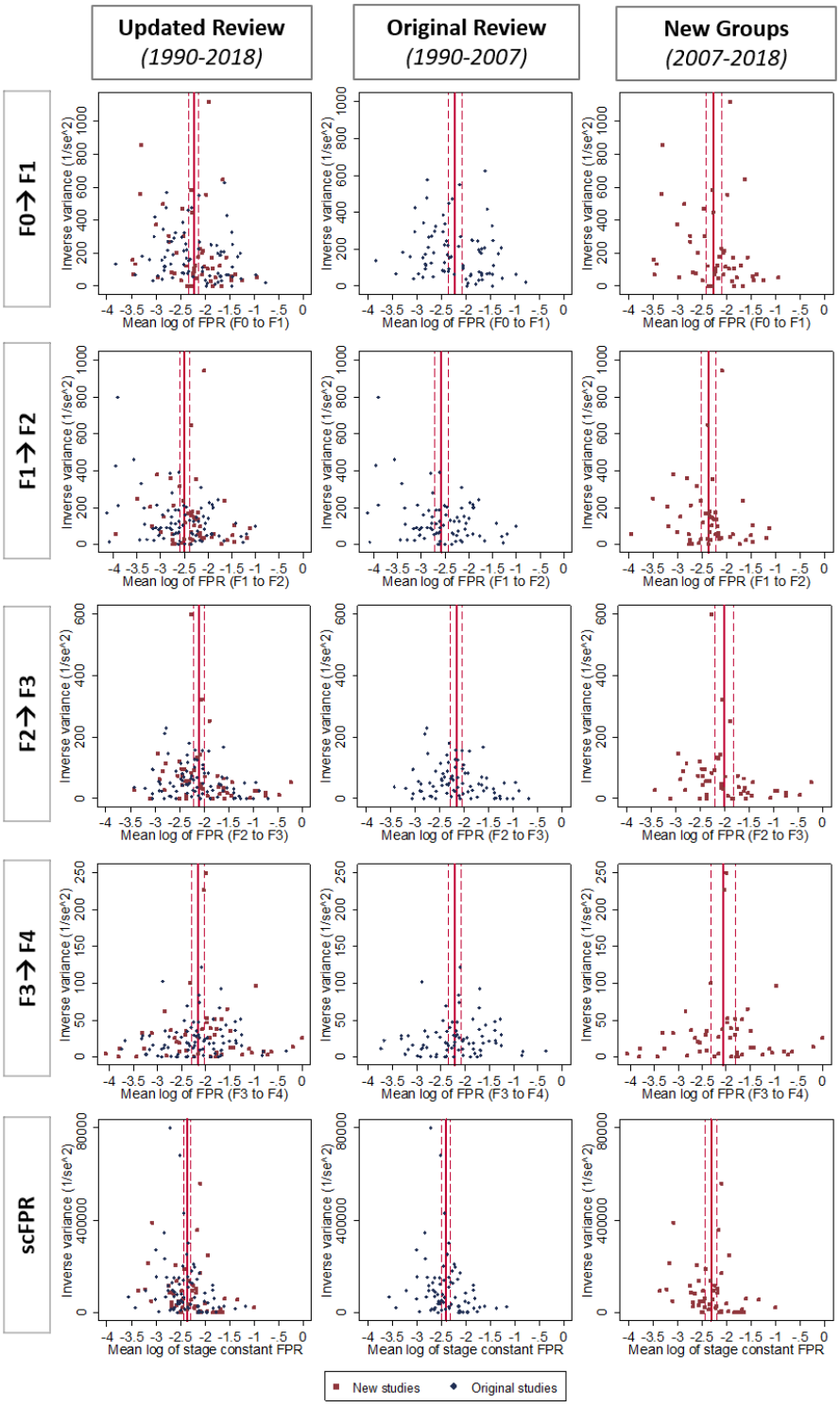
3. S2 Table : Fibrosis scoring systems for HCV
4. S3 Table : Table summarizing study characteristics of the 45 identified studies
5. S4 Table : Table summarizing patient characteristics for the 45 identified
6. List of 45 studies identified by updated systematic review
7. S5 Table : Summary of clinical characteristics of study subjects stratified by review update
8. S6 Table : Hepatic fibrosis progression rates stratified by review update
9. S7 Table : Covariate-adjusted hepatic fibrosis progression rates for CHC subgroups
10. S8 Table : Univariate random effects meta-regression of covariates associated with fibrosis progression
11. Database search strategy and search strings
12. List of extracted data items
13. Supplemental References

Supplementary Materials

S1 Figure : Funnel plots for hepatic fibrosis progression rate



Supplementary Figure 1. Funnel plots of stage-specific and stage-constant (sc) FPRs for the 131 study groups included in the meta-analysis stratified by study update. Funnel plots were generated by plotting the natural log of FPRs against inverse variance.

Supplementary Materials

S1 Table : General definitions of study type, setting, and population

Study design	
Cross-sectional/retrospective:	Patients with liver disease presenting for clinical care, usually at tertiary care centers, where efforts were made to track the liver disease responsible for the referral back to the presumed time of infection, based on the history of receipt of blood or blood product or of the first use of injection drugs [1–17].
Retrospective-prospective:	Studies that identify groups of individuals who, in the past, were either asymptomatic or had developed recognized acute hepatitis C following an outbreak of HCV infection from a recognized source, who could be traced retrospectively, recontacted, and then followed-up prospectively [18–41].
Study setting	
Clinical:	Individuals who were identified and/or assessed for their HCV status and liver disease in a clinical/tertiary care setting [2,3,12,14–16,20,21,23–26,4,27,30,35,36,38,39,41–44,5–11].
Nonclinical:	Individuals who were screened for HCV in a nonclinical setting, for example, blood donation center or regional center [1,13,17–19,22,28,29,37,40].
Study population:	
Community:	HCV-infected individuals identified or participating in national health screening or studies conducted in nonclinical settings [18,45].
Liver clinic:	HCV-infected individuals referred to specialist liver clinics for further assessment [1,4,23–27,30,33,35,39,41,9,42,44,11,12,14–16,20,21].
Blood donors:	Individuals newly diagnosed with chronic HCV infection at blood donor screening [19,37].
Dialysis patients:	HCV-infected individuals with end-stage renal disease receiving dialysis and awaiting renal transplantation [2,31,34].
Injecting drug users:	Individuals who acknowledged injection drug use as the main risk factor for HCV infection – not only active users [17,28,29,40,43].
Female cohorts:	Population of otherwise healthy females infected with HCV [13].
Pediatric population:	Population of children infected with HCV [10,36].
Post-transfusion cohorts:	Population infected with HCV post-transfusion [8,22].
Renal transplant:	Population renal transplant recipients infected with HCV [32,38].
Infectious diseases:	HCV infected individuals managed at Infectious diseases unit [3,5–7].
General:	
Presumed date of HCV infection	Date of transfusion of blood or blood products prior to 1992, when serologic screening for HCV became widely available, the first year of injecting drug use, or the date of a single and convincing parenteral exposure (e.g. needle-stick injury).
Estimated duration of HCV infection	Time elapsed from the presumed date of infection to the date of liver biopsy. Estimated only for individuals with known risk factors.
Elevated ALT levels	ALT values abnormally elevated (more than the upper limit of normal values) at entry and at least once during the 6 months prior to screening.
Excess alcohol consumption	Accepted the definitions reported in the studies. Alcohol consumption of at least more than 20 g/day in the past 12 months of study entry.

Supplementary Table 1. Abbreviations: HCV: Hepatitis C virus; ALT: alanine aminotransferase. References provided for newly identified studies only.

Supplementary Materials

S2 Table : Fibrosis scoring systems for HCV

HCV disease severity	Liver Biopsy (LB)				Transient Elastography (TE)		
	Histological Scoring Systems				Liver Stiffness Measurement (LSM)		
	METAVIR		Knodell	Ishak	LSM cut-off (kPa)	AUROC	References
No fibrosis	**No fibrosis**	**F0**	F0	0	-	-	[46]
Mild fibrosis	**Portal fibrosis without septa**	**F1**	F1	1	<7.1	-	
Moderate fibrosis	**Portal fibrosis with rare septa**	**F2**	F3	2	7.1-9.5	0.83	
Severe fibrosis	**Numerous septa without cirrhosis**	**F3**	F3	3-4	9.5-12.5	0.84	
Cirrhosis	**Cirrhosis**	**F4**	F4	5-6	≥12.5	0.95	

Supplementary Table 2**.** Table showing the critera used to convert various invasive and non-invasive scoring systems to the well-validated METAVIR system .Abbreviations: LB: Liver biopsy; TE: Transient elastography/FibroScan; LSM: Liver stiffness measurement; METAVIR: Meta-analysis of histological data in viral hepatitis; AUROC: Area under the receiver operator curve.

Supplementary Materials

S3 Table : Table summarizing study characteristics of the 45 identified studies

Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
1	**Agostini 2007** [18]	2007	France	English	Community	Non-clinical	R-P	3794	1283	LB	METAVIR	FPR $_{0\to1}$:0.119 FPR $_{1\to2}$:0.182 FPR $_{2\to3}$:0.186 FPR $_{3\to4}$:0.069 ScFPR: 0.137
2	**Allison 2012** [19]	2012	USA	English	Blood donor	Non-clinical	R-P	185	185	LB	Ishak	FPR $_{0\to1}$:0.044 FPR $_{1\to2}$:0.072 FPR $_{2\to3}$:0.047 FPR $_{3\to4}$:0.022 ScFPR: 0.050
3	**Boonwaat 2010** [1]	2010	Australia	English	Liver clinic/prison	Non-clinical	C-S/R	371	153	LB	METAVIR	FPR $_{0\to1}$:0.085 FPR $_{1\to2}$:0.114 FPR $_{2\to3}$:0.148 FPR $_{3\to4}$:0.047 ScFPR: 0.095
4	**Bourliere 2012** [30]	2012	France	English	Liver clinic	Clinical	R-P	2066	1794	LB	METAVIR	FPR $_{0\to1}$:0.118 FPR $_{1\to2}$:0.101 FPR $_{2\to3}$:0.084 FPR $_{3\to4}$:0.111 ScFPR: 0.100
5	**Contreras 2007** [2]	2007	Mexico	English	Dialysis patients	Clinical	C-S/R	64	64	LB	Ishak	FPR $_{0\to1}$:0.113 FPR $_{1\to2}$:0.205 FPR $_{2\to3}$:0.103 FPR $_{3\to4}$:0.123 ScFPR: 0.130
6	**Delgado-Borego 2010** [47]	2010	USA	English	Pediatric	Clinical	C-S/R	102	102	LB	METAVIR	FPR $_{0\to1}$:0.203 FPR $_{1\to2}$:0.071 FPR $_{2\to3}$:0.220 FPR $_{3\to4}$:0.034 ScFPR: 0.131
7	**Forestier 2012** [35]	2012	France	English	Liver clinic	Clinical	R-P	98	45	LB	METAVIR	FPR $_{0\to1}$:0.208 FPR $_{1\to2}$:0.122 FPR $_{2\to3}$:0.123 FPR $_{3\to4}$:0.219 ScFPR: 0.152
8	**Goodman 2008** [36]	2008	USA	English	Pediatric	Clinical	R-P	121	121	LB	Knodell	FPR $_{0\to1}$:0.200 FPR $_{1\to2}$:0.106 FPR $_{2\to3}$:0.038 FPR $_{3\to4}$:0.129 ScFPR: 0.137
9	**Hui 2007** [11]	2007	China	English	Liver clinic	Clinical	C-S/R	82	53	LB	METAVIR	FPR $_{0\to1}$:0.033 FPR $_{1\to2}$:0.042 FPR $_{2\to3}$:0.095 FPR $_{3\to4}$:0.072 ScFPR: 0.041

Supplementary Materials

Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
10a	**Liu 2014 – Marijuana** [12]	2014	Canada	English	Liver clinic	Clinical	C-S/R	102	102	LB	Batts and Ludwig	$FPR_{0\to1}$:0.145 $FPR_{1\to2}$:0.159 $FPR_{2\to3}$:0.083 $FPR_{3\to4}$:0.123 ScFPR: 0.130
10b	**Liu 2014 – Marijuana** [12]	2014	Canada	English	Liver clinic	Clinical	C-S/R	275	275	LB	Batts and Ludwig	$FPR_{0\to1}$:0.145 $FPR_{1\to2}$:0.109 $FPR_{2\to3}$:0.071 $FPR_{3\to4}$:0.102 ScFPR: 0.110
11	**Nanda 2012** [13]	2012	Ireland	English	Female	Non-clinical	C-S/R	20	20	LB	Ishak	$FPR_{0\to1}$:0.023 $FPR_{1\to2}$:0.046 $FPR_{2\to3}$:0.098 $FPR_{3\to4}$:0.164 ScFPR: 0.033
12	**Rao 2012** [37]	2012	China	English	Blood donor	Non-clinical	R-P	348	175	LSM	METAVIR	$FPR_{0\to1}$:0.054 $FPR_{1\to2}$:0.082 $FPR_{2\to3}$:0.116 $FPR_{3\to4}$:0.113 ScFPR: 0.068
13a	**Siddiqui 2008** [14]	2008	USA	English	Liver clinic	Clinical	C-S/R	2035	1009	LB	METAVIR	$FPR_{0\to1}$:0.077 $FPR_{1\to2}$:0.088 $FPR_{2\to3}$:0.143 $FPR_{3\to4}$:0.138 ScFPR: 0.087
13b	**Siddiqui 2008** [14]	2008	USA	English	Liver clinic	Clinical	C-S/R	616	356	LB	METAVIR	$FPR_{0\to1}$: 0.076 $FPR_{1\to2}$:0.102 $FPR_{2\to3}$:0.153 $FPR_{3\to4}$:0.190 ScFPR: 0.93
14	**Werner 2010** [38]	2010	USA	English	Renal transplant	Clinical	R-P	22	22	LB	Batts and Ludwig	$FPR_{0\to1}$:0.293 $FPR_{1\to2}$:0.230 $FPR_{2\to3}$:0.356 $FPR_{3\to4}$:0.336 ScFPR: 0.277
15a	**Bochud 2009** [39]	2009	Switzerland	English	Liver clinic	Clinical	^{14}R-P	607	607	LB	METAVIR	$FPR_{0\to1}$:0.094 $FPR_{1\to2}$:0.067 $FPR_{2\to3}$:0.073 $FPR_{3\to4}$:0.125 ScFPR: 0.080
15b	**Bochud 2009** [39]	2009	Switzerland	English	Liver clinic	Clinical	R-P	90	90	LB	METAVIR	$FPR_{0\to1}$:0.082 $FPR_{1\to2}$:0.84 $FPR_{2\to3}$:0.066 $FPR_{3\to4}$:0.082 ScFPR: 0.077

Supplementary Table 7 continued

Supplementary Materials

Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
15c	**Bochud 2009** [39]	2009	Switzerland	English	Liver clinic	Clinical	R-P	312	312	LB	METAVIR	FPR $_{0\to1}$:0.115 FPR $_{1\to2}$:0.096 FPR $_{2\to3}$:0.080 FPR $_{3\to4}$:0.199 ScFPR: 0.101
15d	**Bochud 2009** [39]	2009	Switzerland	English	Liver clinic	Clinical	R-P	117	117	LB	METAVIR	FPR $_{0\to1}$:0.081 FPR $_{1\to2}$:0.075 FPR $_{2\to3}$:0.080 FPR $_{3\to4}$:0.167 ScFPR: 0.079
16	**Hissar 2009** [15]	2009	India	English	Liver clinic	Clinical	C-S/R	213	213	LB	Knodell	FPR $_{0\to1}$:0.253 FPR $_{1\to2}$:0.166 FPR $_{2\to3}$:0.220 FPR $_{3\to4}$:0.160 ScFPR: 0.192
17	**Kallwitz 2010** [16]	2010	USA	English	Liver clinic	Clinical	C-S/R	812	812	LB	METAVIR	FPR $_{0\to1}$:0.087 FPR $_{1\to2}$:0.162 FPR $_{2\to3}$:0.110 FPR $_{3\to4}$:0.111 ScFPR: 0.099
18	**Kielland 2014** [40]	2014	Norway	English	IDU	Non-clinical	R-P	61	61	LB	METAVIR	FPR $_{0\to1}$:0.122 FPR $_{1\to2}$:0.022 FPR $_{2\to3}$:0.448 FPR $_{3\to4}$:0.270 ScFPR: 0.077
19a	**Larsen 2010** [17]	2010	France	English	IDU	Non-clinical	C-S/R	1077	493	LB	METAVIR	FPR $_{0\to1}$:0.166 FPR $_{1\to2}$:0.104 FPR $_{2\to3}$:0.154 FPR $_{3\to4}$:0.273 ScFPR: 0.133
19b	**Larsen 2010** [17]	2010	France	English	IDU	Non-clinical	C-S/R	1986	1108	LB	METAVIR	FPR $_{0\to1}$:0.138 FPR $_{1\to2}$:0.065 FPR $_{2\to3}$:0.106 FPR $_{3\to4}$:0.267 ScFPR: 0.101
20a	**Lawson 2010** [41]	2010	UK	English	Liver clinic	Clinical	R-P	87	39	LB	Ishak	FPR $_{0\to1}$:0.038 FPR $_{1\to2}$:0.066 FPR $_{2\to3}$:0.158 FPR $_{3\to4}$:0.380 ScFPR: 0.049
20b	**Lawson 2010** [41]	2010	UK	English	Liver clinic	Clinical	R-P	1140	459	LB	Ishak	FPR $_{0\to1}$:0.071 FPR $_{1\to2}$:0.152 FPR $_{2\to3}$:0.342 FPR $_{3\to4}$:0.198 ScFPR: 0.108

Supplementary Table 7 continued

Supplementary Materials

Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
21	**Marabita 2011** [20]	2011	Italy	English	Liver clinic	Clinical	R-P	247	247	LB	Ishak	FPR $_{0\to1}$:0.193 FPR $_{1\to2}$:0.062 FPR $_{2\to3}$:0.067 FPR $_{3\to4}$:0.076 ScFPR : 0.088
22a	**Patin 2012-French cohort** [42]	2012	France	English	Liver clinic	Clinical	R-P	467	467	LB	METAVIR	FPR $_{0\to1}$:0.121 FPR $_{1\to2}$:0.042 FPR $_{2\to3}$:0.530 FPR $_{3\to4}$:0.081 ScFPR : 0.089
22b	**Patin 2012-Swiss cohort** [42]	2012	Switzerland	English	Liver clinic	Clinical	R-P	694	614	LB	METAVIR	FPR $_{0\to1}$:0.093 FPR $_{1\to2}$:0.067 FPR $_{2\to3}$:0.058 FPR $_{3\to4}$:0.905 ScFPR : 0.081
22c	**Patin 2012-US/France** [42]	2012	US/France	English	Liver clinic	Clinical	R-P	320	320	LB	METAVIR	FPR $_{0\to1}$:0.088 FPR $_{1\to2}$:0.063 FPR $_{2\to3}$:0.099 FPR $_{3\to4}$:0.063 ScFPR : 0.076
22d	**Patin 2012-International** [42]	2012	Australia/ Germany/ UK	English	Liver clinic	Clinical	R-P	642	642	LB	METAVIR	FPR $_{0\to1}$:0.103 FPR $_{1\to2}$:0.076 FPR $_{2\to3}$:0.087 FPR $_{3\to4}$:0.139 ScFPR : 0.091
22e	**Patin 2012-Australian** [42]	2012	Australia	English	Liver clinic	Clinical	R-P	219	219	LB	METAVIR	FPR $_{0\to1}$:0.140 FPR $_{1\to2}$:0.088 FPR $_{2\to3}$:0.077 FPR $_{3\to4}$:0.134 ScFPR : 0.102
23	**Brescini 2014**	2014	Italy	English	Infectious diseases	Clinical	C-S/R	186	186	LSM	METAVIR	FPR $_{0\to1}$:0.192 FPR $_{1\to2}$:0.246 FPR $_{2\to3}$:0.421 FPR $_{3\to4}$:0.597 ScFPR : 0.234
24	**de Ledinghen 2008** [4]	2008	Spain	English	Liver clinic	Clinical	C-S/R	656	656	LSM	METAVIR	FPR $_{0\to1}$:0.045 FPR $_{1\to2}$:0.051 FPR $_{2\to3}$:0.109 FPR $_{3\to4}$:0.157 ScFPR : 0.053
25	**Nunnari 2010** [5]	2010	Italy	English	Infectious diseases	Clinical	C-S/R	70	70	LB	METAVIR	FPR $_{0\to1}$:0.157 FPR $_{1\to2}$:0.280 FPR $_{2\to3}$:0.174 FPR $_{3\to4}$:0.099 ScFPR : 0.173

Supplementary Table 7 continued

Supplementary Materials

Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
26	**Mazzocato 2014** [6]	2014	Italy	English	Infectious diseases	Clinical	C-S/R	115	115	LSM	METAVIR	FPR $_{0\to1}$:0.172 FPR $_{1\to2}$:0.192 FPR $_{2\to3}$:0.658 FPR $_{3\to4}$:0.905 ScFPR : 0.216
27	**Suarez-Zarracina 2012** [7]	2012	Spain	English	Infectious diseases	Clinical	C-S/R	68	68	LSM	METAVIR	FPR $_{0\to1}$:0.079 FPR $_{1\to2}$:0.138 FPR $_{2\to3}$:0.124 FPR $_{3\to4}$:0.082 ScFPR : 0.095
28	**White 2012** [21]	2012	USA	English	Liver clinic	Clinical	R-P	308	308	FibroSURE-ActiTest	METAVIR	FPR $_{0\to1}$:0.078 FPR $_{1\to2}$:0.103 FPR $_{2\to3}$:0.092 FPR $_{3\to4}$:0.069 ScFPR : 0.078
29	**Reggiardo 2012** [22]	2012	Argentina	English	Blood transfusion	Non-clinical	R-P	40	40	LB	METAVIR	FPR $_{0\to1}$:0.075 FPR $_{1\to2}$:0.050 FPR $_{2\to3}$:0.128 FPR $_{3\to4}$:0.017 ScFPR : 0.066
30	**Liu 2014** [8]	2014	China	Chinese	Blood transfusion	Clinical	C-S/R	96	52	LSM	METAVIR	FPR $_{0\to1}$: 0.106 FPR $_{1\to2}$: 0.077 FPR $_{2\to3}$:0.154 FPR $_{3\to4}$:0.195 ScFPR : 0.101
31a	**Terrault 2008** [23]	2008	USA	English	Liver clinic	Clinical	R-P	157	157	LB	Ishak	FPR $_{0\to1}$:0.099 FPR $_{1\to2}$:0.080 FPR $_{2\to3}$:0.093 FPR $_{3\to4}$:0.030 ScFPR : 0.081
31b	**Terrault 2008** [23]	2008	USA	English	Liver clinic	Clinical	R-P	143	143	LB	Ishak	FPR $_{0\to1}$:0.100 FPR $_{1\to2}$:0.076 FPR $_{2\to3}$:0.076 FPR $_{3\to4}$:0.017 ScFPR : 0.079
32	**Guyader 2007** [24]	2007	France	English	Liver clinic	Clinical	R-P	586	580	LB	METAVIR	FPR $_{0\to1}$:0.075 FPR $_{1\to2}$:0.085 FPR $_{2\to3}$:0.136 FPR $_{3\to4}$: 0.221 ScFPR : 0.085
33	**Pradat 2007** [25]	2007	France	English	Liver clinic	Clinical	R-P	247	247	LB	METAVIR	FPR $_{0\to1}$:0.237 FPR $_{1\to2}$:0.094 FPR $_{2\to3}$:0.149 FPR $_{3\to4}$:0.064 ScFPR : 0.138

Supplementary Table 7 continued

Supplementary Materials

Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
34a	**Castera 2004** [26]	2004	France	English	Liver clinic	Clinical	R-P	37	37	LB	METAVIR	FPR $_{0\to1}$:0.116 FPR $_{1\to2}$:0.176 FPR $_{2\to3}$:0.110 FPR $_{3\to4}$:0.218 ScFPR : 0.131
34b	**Castera 2004** [26]	2004	France	English	Liver clinic	Clinical	R-P	114	114	LB	METAVIR	FPR $_{0\to1}$:0.080 FPR $_{1\to2}$:0.111 FPR $_{2\to3}$:0.084 FPR $_{3\to4}$:0.175 ScFPR : 0.090
35a	**Mathurin 1998** [27]	1998	France	English	Liver clinic	Clinical	R-P	102	67	LB	METAVIR	FPR $_{0\to1}$:0.081 FPR $_{1\to2}$:0.034 FPR $_{2\to3}$:0.108 FPR $_{3\to4}$:0.281 ScFPR : 0.067
35b	**Mathurin 1998** [27]	1998	France	English	Liver clinic	Clinical	R-P	102	101	LB	METAVIR	FPR $_{0\to1}$:0.200 FPR $_{1\to2}$:0.098 FPR $_{2\to3}$:0.077 FPR $_{3\to4}$:0.201 ScFPR : 0.129
36	**Bruden, 2017**[45]	2017	USA	English	Community	Non-clinical	R-P	407	407	LB	Ishak	FPR $_{0\to1}$:0.091 FPR $_{1\to2}$:0.153 FPR $_{2\to3}$:0.088 FPR $_{3\to4}$:0.062 ScFPR : 0.994
37	**Cepeda, 2016**[28]	2016	Indian	English	IDU	Non-clinical	R-P	281	281	LSM	METAVIR	FPR $_{0\to1}$:0.088 FPR $_{1\to2}$:0.138 FPR $_{2\to3}$:0.242 FPR $_{3\to4}$:0.225 ScFPR : 0.118
38	**Cepeda, 2017**[29]	2017	USA	English	IDU	Non-clinical	R-P	964	964	LSM	METAVIR	FPR $_{0\to1}$:0.042 FPR $_{1\to2}$:0.053 FPR $_{2\to3}$:0.143 FPR $_{3\to4}$:0.113 ScFPR : 0.053
39	**Sakellariou, 2014**[34]	2014	Greece	English	Dialysis patients	Clinical	R-P	61	58	LB	Ishak	FPR $_{0\to1}$:0.322 FPR $_{1\to2}$:0.0822 FPR $_{2\to3}$:0.803 FPR $_{3\to4}$:0.449 ScFPR : 0.238
40a	**Lemos, 2007 A**[31]	2007	Brazil	English	Dialysis patients	Clinical	R-P	39	38	LB	Ludwig	FPR $_{0\to1}$:0.092 FPR $_{1\to2}$:0.154 FPR $_{2\to3}$:0.116 FPR $_{3\to4}$:0.100 ScFPR : 0.105

Supplementary Table 7 continued

Supplementary Materials

Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
40b	**Lemos, 2007 B**[31]	2007	Brazil	English	Dialysis patients	Clinical	R-P	117	117	LB	Ludwig	FPR $_{0\to1}$:0.145 FPR $_{1\to2}$:0.100 FPR $_{2\to3}$:0.485 FPR $_{3\to4}$:0.192 ScFPR : 0.144
41	**Delladetsima, 2013**[32]	2013	Greece	English	Renal transplant	Clinical	R-P	23	29	LB	Ishak	FPR $_{0\to1}$:0.220 FPR $_{1\to2}$:0.102 FPR $_{2\to3}$:0.504 FPR $_{3\to4}$:0.655 ScFPR : 0.196
42	**Besheer, 2017**[33]	2017	Egypt	English	Liver clinic	Clinical	R-P	122	122	LB	METAVIR	FPR $_{0\to1}$:0.150 FPR $_{1\to2}$:0.136 FPR $_{2\to3}$:0.179 FPR $_{3\to4}$:0.127 ScFPR : 0.135
43	**Midgard, 2017**[43]	2017	International	English	Injection drug users	Clinical	R-P	93	122	LB/LSM/APRI	METAVIR	FPR $_{0\to1}$:0.052 FPR $_{1\to2}$:0.058 FPR $_{2\to3}$:0.173 FPR $_{3\to4}$:0.121 ScFPR : 0.062
44	**Chen, 2017**[44]	2017	Australia	English	Liver clinic	Clinical	R-P	131	122	LB	METAVIR	FPR $_{0\to1}$:0.068 FPR $_{1\to2}$:0.081 FPR $_{2\to3}$:0.150 FPR $_{3\to4}$:0.245 ScFPR : 0.081
45	**Valva, 2014**[9]	2014	Argentina	English	Liver clinic	Clinical	C-S/R	32	122	LB	METAVIR	FPR $_{0\to1}$:0.093 FPR $_{1\to2}$:0.163 FPR $_{2\to3}$:0.092 FPR $_{3\to4}$:0.027 ScFPR : 0.098

Supplementary Table 7 continued

Supplementary Table 3. Table summarizing study characteristics for all 45 l studies identified by the updated systematic review. Abbreviations: HCV: Hepatitis C virus; C-S/R: cross-sectional/retrospective; R-P: retrospective-prospective; LB: liver biopsy; LSM: liver stiffness measurement; FPR: fibrosis progression rate; scFPR: stage-constant annual fibrosis progression rate (assuming constant progression over F0 to F4).

Supplementary Materials

S4 Table : Table summarizing patient characteristics for the 45 identified studies

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m^2)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
1	**Agostini 2007**	42.4	62.86	12.00	11.41	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 65.8 BT: 14.4 SP: 19.8	.	10.36	0.00	F0: 24.00 F1: 24.01 F2: 22.62 F3: 22.60 F4: 6.76	.
2	**Allison 2012**	43.1	50.81	25.00	.	100.00	3.32	GT1: 73.5 GT2: 16.8 GT3: 3.8 GT4: 1.1	IDU: 0.0 BT: 100 SP: 0.0	33.76	.	.	F0: 32.97 F1: 26.49 F2: 25.95 F3: 12.43 F4: 2.16	70.22
3	**Boonwaat 2010**	34.0	76.28	15.00	46.05	100.00	.	GT1: 22.9 GT2: 6.7 GT3: 23.7 GT4: 3.0	IDU: 62.0 BT: 2.2 SP: .	.	4.85	8.09	F0: 28.10 F1: 28.76 F2: 19.61 F3: 18.95 F4: 4.58	.
4	**Bourliere 2012**	47.2	61.91	21.00	5.91	100.00	.	GT1: 52.1 GT2: 12.3 GT3: 24.9 GT4: 8.1	IDU: 39.2 BT: 2.2 SP: .	24.40	5.18	1.11	F0: 8.36 F1: 25.08 F2: 31.72 F3: 17.78 F4: 17.06	.
5	**Contreras 2007**	43.5	46.88	10.32	35.94	.	.	GT1: . GT2: . GT3: . GT4: .	IDU: 0.0 BT: 100 SP: 0.0	.	.	0.00	F0: 31.25 F1: 23.44 F2: 29.69 F3: 10.94 F4: 4.69	68.58
6	**Delgado-Borego 2010**	14.8	51.00	12.00	0.00	100.00	.	GT1: 88.2 GT2: 3.9 GT3: 6.9 GT4: 1.0	IDU: 2.0 BT: 4.0 SP : 15.0	.	.	.	F0: 8.80 F1: 52.00 F2: 15.70 F3: 20.60 F4: 2.90	.
7	**Forestier 2012**	54.0	53.06	13.00	.	100.00	6.58	GT1: 84.7 GT2: 3.1 GT3: 9.2 GT4: 3.1	IDU: . BT: . SP: .	26.00	.	.	F0: 6.67 F1 :33.3 F2: 31.11 F3: 13.33 F4: 15.56	59.00

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Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m^2)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
8	**Goodman 2008**	9.8	56.20	9.80	0.00	100.00	.	GT1: 82.6 GT2: 5.8 GT3: 10.7 GT4: .	IDU: 0.0 BT: 7.4 SP: 14.9	20.3	0.00	0.00	F0: 14.05 F1: 45.45 F2: 34.71 F3: 4.13 F4: 1.65	.
9	**Hui 2007**	53.7	82.93	38.00	.	100.00	5.81	GT1: 37.8 GT2: 7.3 GT3: 6.1 GT4: .	IDU: 43.9 BT: 34.2 SP: 22.0	27.94	0.00	0.00	F0: 28.30 F1: 30.19 F2: 13.21 F3: 13.21 F4: 15.09	33.49
10a	**Liu 2014 - Marijuana**	43.9	77.50	14.69	27.45	100.00	2.70	GT1: 81.2 GT2: 4.0 GT3: 14.9 GT4: 0.0	IDU: 74.0 BT: . SP: .	.	8.85	.	F0: 11.9 F1: 22.8 F2: 38.60 F3: 15.80 F4: 10.90	90.30
10b	**Liu 2014 - Marijuana**	46.7	67.60	18.01	11.64	100.00	2.31	GT1: 67.3 GT2: 9.5 GT3: 14.5 GT4: 6.2	IDU: 53.1 BT: . SP: .	.	1.09	.	F0: 7.30 F1: 26.9 F2: 37.8 F3: 6.40 F4: 11.60	98.00
11	**Nanda 2012**	59.0	0.00	30.00	.	100.00	.	GT1: 100 GT2: 0.0 GT3: 0.0 GT4: 0.0	IDU: . BT: 0.0 SP: .	25.30	.	.	F0: 50.00 F1: 25.00 F2: 10.00 F3: 5.00 F4: 10.00	.
12	**Rao 2012**	53.7	44.83	25.20	21.26	100.00	6.22	GT1: 75.6 GT2: 11.2 GT3: . GT4: .	IDU: 0.0 BT: 100 SP: 0.0	.	0.00	1.44	F0: 25.71 F1: 25.14 F2: 17.71 F3: 14.29 F4: 17.14	45.80
13a	**Siddiqui 2008**	50.0	56.61	22.50	.	84.00	.	GT1: 57.5 GT2: 3.2 GT3: 0.9 GT4: 0.4	IDU:52.6 BT: 14.2 SP: 20.3	.	.	2.80	F0: 17.74 F1: 27.16 F2: 17.84 F3: 15.66 F4: 21.61	66.00
13b	**Siddiqui 2008**	45.3	60.55	22.50	.	82.00	.	GT1: 42.5 GT2: 6.5 GT3: 9.9 GT4: 1.3	IDU: 45.3 BT: 16.9 SP : 25.3	.	.	3.41	F0: 18.26 F1: 23.31 F2: 17.42 F3: 13.20 F4: 27.81	77.00

Supplementary Table 8 continued

Supplementary Materials

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m^2)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
14	**Werner 2010**	49.1	72.73	4.43	.	100.00	6.12	GT1: 72.7 GT2: 13.6 GT3: 13.6 GT4: 0.0	IDU: . BT: . SP: .	.	.	.	F0: 27.27 F1: 40.91 F2: 18.18 F3: 9.09 F4:4.55	.
15a	**Bochud 2009**	42.0	60.00	21.00	55.02	100.00	6.00	GT1: 100 GT2: 0.0 GT3: 0.0 GT4: 0.0	IDU: 49.0 BT: 22.0 SP: .	23.90	7.00	0.00	F0: 14.0 F1: 37.0 F2: 27.0 F3: 11.0 F4: 11.0	66.00
15b	**Bochud 2009**	54.0	48.00	24.00	37.78	100.00	5.93	GT1: 0.0 GT2: 100 GT3: 0.0 GT4: 0.0	IDU:11.0 BT: 53.0 SP: .	24.90	2.00	0.00	F0: 14.00 F1: 27.00 F2: 31.00 F3: 16.00 F4: 12.00	45.00
15c	**Bochud 2009**	40.0	65.00	20.00	63.14	100.00	5.90	GT1: 0.0 GT2: 0.0 GT3: 100 GT4: 0.0	IDU:66.0 BT: 9.0 SP: .	23.30	7.00	0.00	F0: 10.00 F1: 28.00 F2: 32.00 F3: 11.00 F4: 19.00	76.00
15d	**Bochud 2009**	41.0	66.00	22.00	56.41	100.00	5.80	GT1: 0.0 GT2: 0.0 GT3: 0.0 GT4: 100	IDU: 60.0 BT: 11.0 SP: .	23.70	7.00	0.00	F0: 17.00 F1: 32.00 F2: 26.00 F3: 10.00 F4: 15.00	63.00
16	**Hissar 2009**	41.6	65.26	12.10	0.00	100.00	4.80	GT1: 11.7 GT2: . GT3: 49.3 GT4: 4.7	IDU: 0.5 BT: 76.1 SP: .	.	0.00	0.00	F0: 4.69 F1: 25.35 F2: 23.94 F3: 24.88 F4: 21.13	118.50
17	**Kallwitz 2010**	49.6	61.00	26.50	.	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 36.5 BT: 33.5 SP: .	30.10	0.00	0.00	F0: 10.0 F1: 10.0 F2: 22.50 F3: 22.50 F4: 35.00	.
18	**Kielland 2014**	37.3	74.5	17.75	.	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 100 BT: 0.0 SP: 0.0	.	0.98	4.90	F0: 11.48 F1: 68.85 F2: 3.28 F3: 4.92 F4: 11.48	.

Supplementary Table 8 continued

Supplementary Materials

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m^2)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
19a	**Larsen 2010**	39.0	75.00	18.00	42.62	100.00	.	GT1: 0.0 GT2: 0.0 GT3: 100 GT4: 0.0	IDU: . BT: . SP: .	.	4.36	1.95	F0: 6.31 F1: 34.34 F2: 28.28 F3: 15.66 F4: 15.40	.
19b	**Larsen 2010**	40.0	75.00	19.00	43.61	100.00	.	GT1: 77.5 GT2: 5.9 GT3: 0.0 GT4: 16.4	IDU: . BT: . SP: .	.	7.05	2.06	F0: 8.30 F1: 46.62 F2: 27.05 F3: 9.63 F4: 8.40	.
20a	**Lawson 2010**	36.0	47.00	14.00	35.63	100.00	.	GT1: 29.9 GT2: 8.1 GT3: 26.4 GT4: .	IDU: 74.7 BT: 12.6 SP: .	22.70	0.00	0.00	F0: 58.32 F1: 25.35 F2: 7.61 F3: 2.54 F4: 5.07	.
20b	**Lawson 2010**	36.0	71.00	14.00	40.44	100.00	.	GT1: 30.9 GT2: 6.1 GT3: 33.8 GT4: .	IDU: 65.4 BT: 11.4 SP: .	25.00	0.00	3.16	F0: 37.02 F1: 22.01 F2: 10.01 F3: 13.95 F4: 17.00	.
21	**Marabita 2011**	47.0	52.23	25.00	0.00	100.00	.	GT1: 52.2 GT2: 30.0 GT3: 13.8 GT4: 4.1	IDU: 23.5 BT: 74.9 SP: .	25.30	0.00	0.00	F0: 0.81 F1: 30.36 F2: 32.39 F3: 20.24 F4: 16.19	.
22a	**Patin 2012-French coh.**	48.2	44.75	20.17	14.56	.	.	GT1: 63.0 GT2: 8.8 GT3: 16.1 GT4: 2.1	IDU: 33.6 BT: 43.9 SP: .	.	0.00	0.00	F0: 8.78 F1: 52.25 F2: 4.28 F3: 19.91 F4: 14.78	.
22b	**Patin 2012-Swiss coh.**	43.6	62.39	22.39	19.02	.	.	GT1: 52.2 GT2: 9.7 GT3: 27.8 GT4: 6.8	IDU: 41.8 BT: 19.2 SP : .	.	0.00	0.00	F0: 12.54 F1: 35.34 F2: 31.27 F3: 0.98 F4: 19.87	.
22c	**Patin 2012-US/France**	48.0	60.31	23.48	11.88	100.00	.	GT1: 67.2 GT2: 5.3 GT3: 16.9 GT4: 4.4	IDU: 7.8 BT: 4.7 SP : .	.	0.00	0.00	F0: 12.81 F1: 35.63 F2: 21.88 F3: 19.06 F4: 10.63	.

Supplementary Table 8 continued

Supplementary Materials

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m^2)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
22d	**Patin 2012-International**	45.8	40.65	16.96	.	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 20.6 BT: 5.1 SP : .	.	0.00	0.00	F0: 17.45 F1: 38.47 F2: 25.23 F3: 10.12 F4: 8.72	.
22e	**Patin 2012-Australian**	62.4	70.78	20.20	.	100.00	.	GT1: 100 GT2: 0.0 GT3: 0.0 GT4: 0.0	IDU: 0 BT: 0 SP : .	.	0.00	0.00	F0: 5.94 F1: 29.68 F2: 33.33 F3: 14.61 F4: 16.44	.
23	**Brescini 2014**	45.0	62.37	6.25	15.05	.	5.76	GT1: 48.9 GT2: 12.4 GT3: 24.7 GT4: 4.3	IDU: 47.9 BT: . SP: .	.	0.00	0.00	F0: 30.11 F1: 30.65 F2: 16.13 F3: 9.14 F4: 13.98	58.00
24	**de Ledinghen 2008**	52.8	38.41	23.50	0.00	100.00	5.83	GT1: 60.4 GT2: 20.1 GT3: 8.8 GT4: 9.5	IDU:16.0 BT: 33.8 SP : .	.	0.00	0.00	F0: 34.60 F1: 34.45 F2: 13.41 F3: 7.16 F4: 10.37	59.00
25	**Nunnari 2010**	52.5	57.14	12.40	.	100.00	2.80	GT1: 71.4 GT2: 14.3 GT3: 14.3 GT4: 0.0	IDU: . BT: . SP : .	.	0.00	0.00	F0: 14.29 F1: 14.29 F2: 28.57 F3: 28.57 F4: 14.29	97.40
26	**Mazzocato 2014**	48.0	58.26	6.00	18.26	.	.	GT1: 38.3 GT2: 18.3 GT3: 13.9 GT4: 2.6	IDU:32.2 BT: . SP: .	.	0.00	0.00	F0: 35.65 F1: 34.78 F2: 9.57 F3: 4.35 F4: 15.65	56.00
27	**Suarez-Zarracina 2012**	46.5	61.76	23.00	64.71	100.00	5.87	GT1: 82.4 GT2: 1.5 GT3: 11.8 GT4: 2.9	IDU: 48.5 BT: 50.0 SP: 0.0	.	0.00	0.00	F0: 16.18 F1: 16.18 F2: 22.06 F3: 25.00 F4: 20.59	85.50
28	**White 2012**	57.0	100.00	34.00	34.09	100.00	6.35	GT1: 85.7 GT2: 8.4 GT3: 4.5 GT4: 0.6	IDU: 50.7 BT: 17.5 SP: .	.	0.00	0.00	F0: 7.14 F1: 12.66 F2: 21.43 F3: 26.95 F4: 31.82	.

Supplementary Table 8 continued

Supplementary Materials

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m^2)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
29	**Reggiardo 2012**	52.5	37.50	21.50	32.50	100	.	GT1: 50.0 GT2: 37.5 GT3: 12.5 GT4: 0.0	IDU: 0.0 BT: 100 SP: 0.0	.	0.00	0.00	F0: 20.00 F1: 42.50 F2: 15.00 F3: 20.00 F4: 2.50	.
30	**Liu 2014**	33.6	43.75	10.22	.	.	6.22	GT1: 69.8 GT2: . GT3: . GT4: .	IDU: 0.0 BT: 100 SP : 0.0	.	.	1.04	F0: 33.65 F1: 42.31 F2: 13.46 F3: 5.77 F4: 3.85	116.00
31a	**Terrault 2008**	46.6	64.33	25.50	0.00	100.00	.	GT1: 100 GT2: 0.0 GT3: 0.0 GT4: 0.0	IDU: 61.8 BT: 26.8 SP: 0.0	.	0.00	0.00	F0: 8.00 F1: 26.00 F2: 25.50 F3: 31.00 F4: 9.00	110.40
31b	**Terrault 2008**	47.9	66.43	24.00	0.00	100.00	.	GT1: 100 GT2: 0.0 GT3: 0.0 GT4: 0.0	IDU: 57.3 BT: 23.1 SP : 0.0	.	0.00	0.00	F0: 9.00 F1: 29.50 F2: 29.50 F3: 28.00 F4: 4.00	66.00
32	**Guyader 2007**	41.6	58.00	16.00	36.00	100.00	.	GT1: 39.5 GT2: 6.8 GT3: 15.0 GT4:.	IDU: 33.0 BT: 34.0 SP : 33.0	23.00	0.00	0.00	F0: 30.00 F1: 33.00 F2: 17.00 F3: 8.00 F4: 11.00	.
33	**Pradat 2007**	39.5	63.97	14.50	15.38	100.00	.	GT1: 35.6 GT2: . GT3: . GT4: .	IDU: . BT: . SP : .	.	.	.	F0: 3.24 F1: 37.25 F2: 25.10 F3: 25.51 F4: 8.91	.
34a	**Castera 2004**	34.4	83.78	12.10	.	100.00	9.30	GT1: 0.0 GT2: 0.0 GT3: 100 GT4: 0.0	IDU: 65.0 BT: 16.0 SP: 19.0	18.10	0.00	0.00	F0: 24.50 F1: 24.50 F2: 30.0 F3: 10.50 F4: 10.50	118.00
34b	**Castera 2004**	45.7	70.18	15.60	.	100.00	6.10	GT1: 78.9 GT2: 15.0 GT3: 0.0 GT4: 3.1	IDU: 14.0 BT: 41.0 SP: 45.0	32.90	0.00	0.00	F0: 28.50 F1: 28.50 F2: 26.0 F3: 8.50 F4: 8.50	143.00

Supplementary Table 8 continued

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Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m^2)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
35a	**Mathurin 1998**	43.0	40.20	14.90	10.78	65.00	.	GT1: 43.1 GT2: 7.8 GT3: 4.9 GT4: 1.0	IDU: 32.0 BT: 35.0 SP: .	.	0.00	0.00	F0: 29.85 F1: 52.24 F2: 10.45 F3: 2.99 F4: 4.48	24.50
35b	**Mathurin 1998**	44.0	40.20	14.10	10.78	80.00	.	GT1: 45.1 GT2: 4.9 GT3: 11.8 GT4: 3.9	IDU: 31.0 BT: 40.0 SP: .	.	0.00	0.00	F0: 5.94 F1: 37.62 F2: 35.64 F3: 9.00 F4: 10.89	140.00
36	**Bruden, 2017**	41.2	4864	18.60	8.85	100.00	.	GT1:68.80 GT2:14.74 GT3:13.27 GT4: 0.41	IDU: 58.7 BT: 14.0 SP: 27.3	.	0.00	0.00	F0: 18.43 F1: 18.42 F2: 32.19 F3: 21.62 F4: 9.34	.
37	**Cepeda, 2016**	41.6	100.00	16.90	67.97	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 100 BT: 0.0 SP: 0.0	19.80	30.25	4.62	F0: 22.42 F1: 22.78 F2: 14.23 F3: 14.23 F4: 26.33	49.00
38	**Cepeda, 2017**	49.0	71.58	27.50	26.21	100.00	6.40	GT1: . GT2: . GT3: . GT4: .	IDU: 100 BT: 0.0 SP: 0.0	.	34.96	.	F0: 31.33 F1: 31.33 F2: 11.31 F3: 11.31 F4: 14.73	.
39	**Sakellariou, 2014**	45.7	60.66	4.20	0.00	100.00	5.06	GT1: 27.9 GT2: 1.6 GT3: 23.0 GT4: 14.8	IDU: . BT: . SP: .	.	0.00	0.00	F0: 25.86 F1: 60.34 F2: 5.17 F3: 5.17 F4: 3.45	.
40a	**Lemos, 2007 A**	57.0	64.10	22.00	0.00	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 0 .0 BT: 69.2 SP: 0.0	.	0.00	0.00	F0: 12.82 F1: 14.10 F2: 24.36 F3: 23.08 F4: 23.10	.
40b	**Lemos, 2007 B**	45.0	62.39	6.00	0.00	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 0.0 BT: 25.6 SP: 0.0	.	0.00	0.00	F0: 41.88 F1: 41.88 F2: 6.84 F3: 6.84 F4: 2.6	.

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Supplementary Table 8 continued														
Study ID	**Study**	**Age (yrs)**	**Gender (%Male)**	**DOI (yrs)**	****Excess alcohol use (%)**	**HCV RNA+ (%)**	**HCV RNA load (log 10 IU/ml)**	**Genotype (%)**	**Mode of Infection (%)**	**BMI (kg/m^2)**	**HIV (%)**	**HBV (%)**	**METAVIR (%)**	**Mean ALT (IU/L)**
41	**Delladetsima, 2013**	42.7	60.87	4.40	.	87.00	3.50	GT1: 47.8 GT2: 0.0 GT3: 26.1 GT4: 13.0	IDU: . BT: . SP: .	.	.	.	F0: 47.83 F1: 60.87 F2: 8.70 F3: 4.35 F4: 4.35	.
42	**Besheer, 2017**	49.5	63.11	19.00	.	100.00	5.79	GT1: . GT2: . GT3: . GT4: .	IDU: . BT: . SP: .	.	.	.	F0: 5.73 F1: 18.85 F2: 19.67 F3: 25.41 F4: 30.33	55.50
43	**Midgard, 2017**	41.0	82.80	21.00	16.13	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 100 BT: 0.0 SP: 0.0	.	0.00	0.00	F0: 33.33 F1: 34.41 F2: 10.75 F3: 10.75 F4: 10.75	.
44	**Chen, 2017**	37.0	69.47	17.00	.	100.00	6.10	GT1: . GT2: . GT3: . GT4: .	IDU:31.3 BT: 16.8 SP: 18.3	25.20	0.00	0.00	F0: 31.30 F1: 32.82 F2: 15.27 F3: 7.63 F4: 12.98	94.00
45	**Valva, 2014**	51.0	65.63	20.00	.	100.00	5.74	GT1: . GT2: . GT3: . GT4: .	IDU: 21.9 BT: 12.5 SP: 62.5	.	0.00	0.00	F0: 15.63 F1: 15.63 F2: 31.25 F3: 31.25 F4: 6.25	67.00
Supplementary Table 8 continued														

Supplementary Table 4. Table summarizing patient characteristics for all 45 studies identified by the updated systematic review. Abbreviations: HCV: Hepatitis C virus; DOI: duration of infection; ALT: alanine aminotransferase; BMI: body mass index; HIV: Human immunodeficiency virus; HBV: Hepatitis B virus; GT: genotype BT: blood transfusion; IDU: intravenous drug use; SP: Sporadic risk. N

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List of 45 studies identified by updated systematic review ordered by study ID:

1. Agostini, H., Castera, L., Melin, P., Cattan, L. & Roudot-Thoraval, F. HEPACOM: multicenter, observational prospective study of outcome and monitoring of HCV positive antiviral-naive patients managed in the French health care system. *Gastroenterologie clinique et biologique* **31,** 1074–1080 (2007).

2. Allison, R. D. *et al.* A 25-year study of the clinical and histologic outcomes of hepatitis C virus infection and its modes of transmission in a cohort of initially asymptomatic blood donors. **206,** 654–661 (2012).

3. Boonwaat, L., Haber, P. S., Levy, M. H. & Lloyd, A. R. Establishment of a successful assessment and treatment service for Australian prison inmates with chronic hepatitis C. *Med J Aust* **192,** 496–500 (2010).

4. Bourliere, M. *et al.* Pegylated interferon-alpha2a plus ribavirin for chronic hepatitis C in a real-life setting: the Hepatys French cohort (2003-2007). *Antivir Ther* **17,** 101–110 (2012).

5. Contreras, A. M. *et al.* End-stage renal disease and hepatitis C infection: comparison of alanine aminotransferase levels and liver histology in patients with and without renal damage. *Annals of hepatology* **6,** 48–54 (2007).

6. Delgado-Borrego, A. *et al.* Influence of body mass index on outcome of pediatric chronic hepatitis C virus infection. *J Pediatr Gastroenterol Nutr* **51,** 191–197 (2010).

7. Forestier, N. *et al.* Acoustic radiation force impulse imaging for evaluation of antiviral treatment response in chronic hepatitis C. *J. Gastrointest. Liver Dis.* **21,** 367–373 (2012).

8. Goodman, Z. D. *et al.* Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial. *Hepatology* **47,** 836–843 (2008).

9. Hui, C.-K. *et al.* Disease progression in Chinese chronic hepatitis C patients with persistently normal alanine aminotransaminase levels. *Alimentary pharmacology & therapeutics* **25,** 1283–1292 (2007).

10. Liu, T. *et al.* Marijuana use in hepatitis C infection does not affect liver biopsy histology or treatment outcomes. **28,** 381–384 (2014).

11. Nanda, K. S. *et al.* Elevated circulating osteoprotegerin and reduced matrix-metalloprotease-9 in post-menopausal women with chronic Hepatitis C virus infection. *Cytokine* **60,** 328–333 (2012).

12. Rao, H.-Y. *et al.* Outcome of hepatitis C virus infection in Chinese paid plasma donors: a 12-19-year cohort study. *Journal of gastroenterology and hepatology* **27,** 526–532 (2012).

13. Siddiqui, F. A. *et al.* Demographics of a large cohort of urban chronic hepatitis C patients. *Hepatology international* **2,** 376–381 (2008).

14. Werner, T. *et al.* Treatment of hepatitis C in renal transplantation candidates: a single-center experience. *Transplantation* **90,** 407–411 (2010).

15. Bochud, P.-Y. *et al.* Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. *J. Hepatol.* **51,** 655–66 (2009).

16. Hissar, S. S. *et al.* Natural history of hepatic fibrosis progression in chronic hepatitis C virus infection in India. *J Gastroenterol Hepatol* **24,** 581–587 (2009).

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17. Kallwitz, E. R. *et al.* Ethnicity and body mass index are associated with hepatitis C presentation and progression. *Clin Gastroenterol Hepatol* **8,** 72–78 (2010).

18. Kielland, K. B. *et al.* Liver fibrosis progression at autopsy in injecting drug users infected by hepatitis C: a longitudinal long-term cohort study. *J Hepatol* **60,** 260–266 (2014).

19. Larsen, C. *et al.* Hepatitis C virus genotype 3 and the risk of severe liver disease in a large population of drug users in France. *J Med Virol* **82,** 1647–1654 (2010).

20. Lawson, A. & Trent Hepatitis, C. S. G. Hepatitis C virus-infected patients with a persistently normal alanine aminotransferase: do they exist and is this really a group with mild disease? *J Viral Hepat* **17,** 51–58 (2010).

21. Marabita, F. *et al.* Genetic variation in the interleukin-28B gene is not associated with fibrosis progression in patients with chronic hepatitis C and known date of infection. *Hepatology* **54,** 1127–1134 (2011).

22. Patin, E. *et al.* Genome-wide association study identifies variants associated with progression of liver fibrosis from HCV infection. *Gastroenterology* **143,** 1212–1244 (2012).

23. Brescini, L. *et al.* Evaluating Liver Fibrosis by Transient Elastometry in Patients With HIV-HCV Coinfection and Monoinfection. *Hepat. Mon.* **14,** e15426 (2014).

24. de Lédinghen, V. *et al.* Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy. *J. Viral Hepat.* **15,** 427–33 (2008).

25. Nunnari, G. Circulating fibrocytes as a marker of liver fibrosis in chronic hepatitis C. *Front. Biosci.* **E2,** 1241 (2010).

26. Mazzocato, S. *et al.* Comparison of liver fi brosis progression in HIV / HCV co-infected and HCV mono-infected patients by transient elastometry. **39,** 797–802 (2014).

27. Suárez-Zarracina, T. *et al.* Didanosine (ddI) associates with increased liver fibrosis in adult HIV-HCV coinfected patients. *J. Viral Hepat.* **19,** 685–93 (2012).

28. White, D. L. *et al.* Higher serum testosterone is associated with increased risk of advanced hepatitis C-related liver disease in males. *Hepatology* **55,** 759–68 (2012).

29. Reggiardo, M. V. *et al.* Natural history of hepatitis C virus infection in a cohort of asymptomatic post-transfused subjects. *Ann. Hepatol.* **11,** 658–66

30. Liu, S., Cheng, M., Mu, M. & Yang, Q. [Natural clearance of hepatitis C virus in 96 patients with infection acquired by blood transfusion from a single donor in Guizhou]. *Zhonghua Gan Zang Bing Za Zhi* **22,** 251–4 (2014).

31. Terrault, N. A. *et al.* Fibrosis progression in African Americans and Caucasian Americans with chronic hepatitis C. *Clin Gastroenterol Hepatol* **6,** 1403–1411 (2008).

32. Guyader, D. *et al.* Liver iron is a surrogate marker of severe fibrosis in chronic hepatitis C. *J. Hepatol.* **46,** 587–95 (2007).

33. Pradat, P., Voirin, N., Tillmann, H. L., Chevallier, M. & Trépo, C. Progression to cirrhosis in hepatitis C patients: An age-dependent process. *Liver Int.* **27,** 335–339 (2007).

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34. Castéra, L. *et al.* Effect of antiviral treatment on evolution of liver steatosis in patients with chronic hepatitis C: indirect evidence of a role of hepatitis C virus genotype 3 in steatosis. *Gut* **53,** 420–4 (2004).

35. Mathurin, P. Slow progression rate of fibrosis in hepatitis C virus patients with persistently normal alanine transaminase activity. *Hepatology* **27,** 868–872 (1998)

36. Bruden DJ, McMahon BJ, Townshend-Bulson L, et al. Risk of End Stage Liver Disease, Hepatocellular Carcinoma and Liver-Related Death By Fibrosis Stage in the Hepatitis C Alaska Cohort. Hepatology. 2017. doi:10.1002/hep.29115.

37. Cepeda JA, Thomas DL, Astemborski J, Kong X, Kirk GD, Mehta SH. Liver disease progression in a community-based sample of HCV-infected PWID. Top Antivir Med. 2016;24 (E-1):218.

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41. Delladetsima I, Psichogiou M, Sypsa V, Sakellariou S, Hatzakis A, J NB. Time of acquisition of HCV infection in renal transplant recipients: a major prognostic factor for disease progression. Clin Transpl. 2013;27(1):72-79. doi:10.1111/ctr.12012.

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44. Chen Yi Mei SLG, Thompson AJ, Christensen B, et al. Sustained virological response halts fibrosis progression : A long-term follow-up study of people with chronic hepatitis C infection. PLoS ONE 12(10). 2017;12(10):1-12.

45. Valva P, Gismondi MI, Casciato PC, et al. Distinctive intrahepatic characteristics of paediatric and adult pathogenesis of chronic hepatitis C infection. *Clin Microbiol Infect*. 2014;20(12):O998-O1009. doi:10.1111/1469-0691.12728.

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S5 Table : Summary of clinical characteristics of study subjects stratified by review update

	Updated Review (1990-2018)			Original Review (1990-2007)			New Groups (2007-2018)		
	N	**Mean**	**SE**	N	**Mean**	**SE**	N	**Mean**	**SE**
Sample size	131	326	35.9	81	315	43.4	50	344	63.1
Male (%)	131	62.0	1.5	81	62.1	2.0	50	61.9	2.1
Age at assessment (yrs.)	131	44.3	0.6	81	44.3	0.5	50	44.4	1.3
Estimated age at infection (yrs.)	131	25.8	0.5	81	25.8	0.4	50	25.8	1.3
Estimated duration of infection (yrs.)	131	18.4	0.5	81	18.5	0.5	50	18.2	1.0
Cirrhosis (%)	131	12.0	0.7	81	11.3	0.8	50	13.2	1.2
Steatosis (%)	39	50.3	3.9	21	48.9	4.4	18	52	6.8
BMI (kg/m^2)	49	25.7	0.4	30	26.1	0.4	19	25	0.9
HIV (%)	106	2.0	0.7	63	1.5	0.8	43	2.8	1.1
HBV (HBsAg positive, %)	104	0.4	0.1	64	0.3	0.1	40	0.6	0.3
Elevated ALT (%)	52	76.2	4.0	37	80.8	4.0	15	65	9.2
ALT (IU/L)	58	87.5	4.3	35	94.3	5.9	23	77.3	5.7
Excess alcohol use (%)	102	19.9	2.1	67	18.1	2.5	35	23.2	3.7
Mode of infection									
IDU (%)	110	43.4	2.5	68	43	2.8	42	44.1	5.0
BT (%)	107	25.7	2.0	68	27.1	2.1	39	23.4	4.0
Sporadic (%)	90	22.4	2.0	68	25.4	2.3	22	13.2	3.8
HCV RNA load (log_{10}IU/mL)	49	5.8	0.2	27	6.1	0.2	22	5.5	0.3
Genotype									
Genotype 1 (%)	113	56.2	2.4	71	57.2	2.4	42	54.5	4.9
Genotype 2 (%)	89	9.5	1.3	49	8.7	0.9	40	10.4	2.6
Genotype 3 (%)	95	17.6	2.0	54	15	1.3	41	21.1	4.3
Genotype 4 (%)	70	4.6	1.5	34	3.4	0.7	36	5.7	2.8
Racial groups									
White (%)	68	68.6	4.3	34	67.2	5.2	34	70	6.9
Black (%)	54	13.4	3.4	30	15.7	4.4	24	10.5	5.5
Asian (%)	47	5.4	3.0	24	5.7	4.1	23	5.1	4.3

Supplementary Table 5. Summary of clinical characteristics of study subjects included in the meta-analysis stratified by review update. Meta-analysis was restricted to study groups where all subjects were confirmed by HCV RNA testing (N=131). Abbreviations: BMI: body mass index; ALT: alanine aminotransferase; IDU: injection drug use; BT: blood transfusion: HCV: hepatitis C virus; HIV: human immunodeficiency virus; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; RNA: ribonucleic acid; N: number of groups in meta-analysis reporting parameter; SE: standard error.

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S6 Table : Hepatic fibrosis progression rates stratified by review update

	Updated Review (1990-2018)					Original Review (1990-2007)				
	N	Mean	95% CI		I^2	N	Mean	95% CI		I^2
[1] All identified groups										
F0 → F1	171	0.112	0.103	0.122	98%	111	0.117	0.104	0.130	98%
F1 → F2	171	0.088	0.080	0.097	98%	111	0.085	0.075	0.096	98%
F2 → F3	171	0.123	0.113	0.133	94%	111	0.120	0.109	0.133	91%
F3 → F4	171	0.120	0.108	0.132	89%	111	0.116	0.104	0.129	83%
scFPR	171	0.099	0.093	0.104	85%	111	0.103	0.098	0.108	85%
[2] HCV RNA+ groups										
F0 → F1	131	0.107	0.097	0.118	98%	81	0.108	0.095	0.123	98%
F1 → F2	131	0.082	0.074	0.091	97%	81	0.076	0.066	0.087	98%
F2 → F3	131	0.117	0.107	0.129	94%	81	0.111	0.099	0.124	89%
F3 → F4	131	0.116	0.104	0.131	89%	81	0.111	0.098	0.125	83%
scFPR	131	0.094	0.088	0.100	85%	81	0.091	0.084	0.098	83%

Supplementary Table 6. Annual stage-specific and stage-constant fibrosis progression rates based on random effect meta-analyses of [1] all identified study groups meeting inclusion/exclusion criteria (N=171); or [2] subset of identified groups where CHC was confirmed by HCV RNA testing in all subjects (N=131) stratified by review update. Hepatic fibrosis stages were based on METAVIR fibrosis scoring system. Abbreviations: CHC: chronic hepatitis C; scFPR: stage-constant annual fibrosis progression rate (assuming constant progression over F0 to F4); I^2: indicates the percentage of variability in estimates due to heterogeneity vs. sampling error; N: number of groups included in the meta-analyses.

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S7 Table : Covariate-adjusted hepatic fibrosis progression rates for CHC subgroups

	F0 → F1			F1 → F2			F2 → F3			F3 → F4			scFPR			TTC*
	Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI		(yrs)
All groups	0.107	0.099	0.115	0.082	0.075	0.090	0.119	0.110	0.129	0.116	0.105	0.129	0.096	0.092	0.100	38
Study design																
Cross-sectional/Retrospective	0.110	0.100	0.122	0.081	0.072	0.092	0.119	0.107	0.132	0.115	0.100	0.132	0.096	0.091	0.101	39
Retrospective-Prospective	0.101	0.086	0.118	0.084	0.069	0.103	0.119	0.100	0.141	0.120	0.097	0.148	0.097	0.089	0.105	39
Study population**																
Females	0.063	0.039	0.103	0.073	0.040	0.136	0.115	0.067	0.199	0.071	0.035	0.144	0.076	0.058	0.100	52
Blood donors	0.102	0.059	0.176	0.060	0.030	0.120	0.088	0.047	0.166	0.059	0.025	0.138	0.081	0.058	0.114	55
Pediatric patients	0.233	0.119	0.459	0.094	0.041	0.218	0.114	0.051	0.254	0.080	0.023	0.283	0.151	0.093	0.245	36
Post transfusion	0.131	0.056	0.305	0.085	0.030	0.247	0.125	0.046	0.341	0.062	0.015	0.247	0.116	0.066	0.204	44
Liver clinic	0.106	0.096	0.117	0.083	0.073	0.095	0.116	0.104	0.129	0.119	0.104	0.136	0.096	0.091	0.100	38
Injection drug users	0.125	0.079	0.197	0.053	0.030	0.094	0.116	0.069	0.193	0.206	0.111	0.380	0.095	0.076	0.120	40
Community	0.133	0.085	0.207	0.098	0.057	0.171	0.118	0.076	0.183	0.145	0.086	0.242	0.109	0.091	0.130	33
Dialysis patients	0.094	0.061	0.144	0.048	0.028	0.083	0.156	0.090	0.271	0.108	0.056	0.209	0.076	0.056	0.103	47
Renal transplant	0.105	0.063	0.174	0.108	0.057	0.203	0.124	0.067	0.228	0.082	0.034	0.202	0.112	0.076	0.164	39
Infectious diseases	0.082	0.049	0.137	0.114	0.059	0.219	0.151	0.086	0.266	0.147	0.075	0.291	0.095	0.071	0.126	34
Publication year																
<2000	0.070	0.042	0.117	0.064	0.034	0.123	0.112	0.059	0.213	0.199	0.091	0.437	0.073	0.052	0.101	44
2000 to <2005	0.106	0.092	0.121	0.073	0.061	0.086	0.112	0.097	0.129	0.115	0.096	0.137	0.091	0.085	0.097	41
2005 to <2010	0.115	0.099	0.135	0.092	0.076	0.112	0.112	0.095	0.131	0.110	0.090	0.134	0.100	0.092	0.107	38
≥2010	0.105	0.087	0.127	0.092	0.073	0.116	0.141	0.116	0.172	0.120	0.093	0.153	0.104	0.095	0.114	36
HCV genotype																
Genotype-1	0.127	0.104	0.155	0.069	0.054	0.089	0.098	0.080	0.121	0.098	0.076	0.126	0.093	0.084	0.102	43
Genotype non-1	0.082	0.062	0.108	0.102	0.071	0.144	0.160	0.120	0.215	0.139	0.097	0.199	0.099	0.086	0.113	35
Genotype-3	0.099	0.064	0.153	0.105	0.061	0.183	0.128	0.081	0.204	0.164	0.094	0.286	0.106	0.086	0.130	34
Genotype non-3	0.103	0.090	0.117	0.082	0.070	0.096	0.124	0.108	0.143	0.113	0.095	0.133	0.095	0.089	0.101	39
Race																
White	0.117	0.099	0.138	0.076	0.062	0.093	0.107	0.090	0.127	0.120	0.097	0.149	0.094	0.087	0.103	39
Black	0.074	0.044	0.122	0.110	0.059	0.207	0.146	0.086	0.248	0.062	0.032	0.122	0.096	0.075	0.123	46
Asian	0.109	0.052	0.227	0.103	0.041	0.261	0.148	0.062	0.353	0.295	0.098	0.891	0.107	0.067	0.172	29

Supplementary Table 7. Annual fibrosis progression rates adjusted for study design, population, publication year, age at HCV infection (mean: 26), duration of infection (mean: 17.6), male gender (mean: 62%), infection by IDU (mean: 43%), infection by blood transfusion (mean: 26%), excess alcohol consumption (mean: 18%), HIV positivity (mean: 2%), genotype-1 (mean: 56%), genotype-3 (mean:17%) and race (69% White; 13% Black and 5% Asian) except the following groups: † pediatric subgroup was adjusted for age at infection at 1.4 and duration of infection at 11 years; †† female subgroup was not adjusted by the mean gender (male gender: 0%); and *post-transfusion cohort was adjusted for the mode of infection by IDU at 0% and blood transfusion at 100%; IDU cohort was adjusted for the mode of infection by IDU at 100% and blood transfusion at 0%. Abbreviations: scFPR: stage-constant annual fibrosis progression rate (assuming constant progression over F0 to F4); *TTC: time-to-cirrhosis (based on adjusted stage-specific annual progression rates); CHC: chronic hepatitis C; HCV: hepatitis C virus.

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S8 Table: Univariate random effects meta-regression of covariates associated with fibrosis progression

	F0→F1*				F1→F2*				F2→F3*				F3→F4*				scFPR*			
Predictors	**β**	**SE**	**P-value**	**RR**	**β**	**SE**	**P-value**	**RR**	**β**	**SE**	**P-value**	**RR**	**β**	**SE**	**P-value**	**RR**	**β**	**SE**	**P-value**	**RR**
Study setting																				
Clinical (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
Non-clinical	-0.383	0.132	**0.004**	***0.68***	-0.287	0.137	**0.039**	***0.75***	-0.055	0.134	0.683	*0.95*	-0.128	0.162	0.432	*0.88*	-0.221	0.085	**0.011**	***0.80***
Study design																				
Cross-sectional/Retrospective (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
Retrospective-Prospective	-0.206	0.105	0.051	*0.81*	-0.004	0.109	0.970	*1.00*	-0.057	0.104	0.585	*0.94*	-0.078	0.125	0.531	*0.92*	-0.102	0.066	0.128	*0.90*
Study population																				
Liver clinic (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
Females	-0.798	0.240	**0.001**	***0.45***	-0.467	0.252	0.067	*0.63*	-0.408	0.245	0.098	*0.67*	-0.779	0.313	**0.014**	***0.46***	-0.561	0.158	**0.001**	***0.57***
Blood donors	-0.458	0.304	0.135	*0.63*	-0.520	0.322	0.109	*0.59*	-0.209	0.329	0.526	*0.81*	-0.685	0.411	0.098	*0.50*	-0.355	0.214	0.099	*0.70*
Pediatric patients	0.642	0.371	0.086	*1.90*	0.064	0.379	0.866	*1.07*	-0.076	0.395	0.848	*0.93*	-0.643	0.598	0.284	*0.53*	0.365	0.283	0.199	*1.44*
Post-transfusion	-0.429	0.373	0.253	*0.65*	-0.055	0.387	0.887	*0.95*	0.066	0.376	0.861	*1.07*	-0.162	0.478	0.735	*0.85*	-0.171	0.242	0.480	*0.84*
Injecting drug users	0.026	0.172	0.881	*1.03*	-0.145	0.177	0.413	*0.87*	0.092	0.170	0.590	*1.10*	0.543	0.197	**0.007**	***1.72***	0.020	0.103	0.849	*1.02*
Community	0.235	0.262	0.372	*1.26*	0.073	0.266	0.785	*1.08*	0.011	0.242	0.963	*1.01*	0.170	0.274	0.537	*1.18*	0.122	0.142	0.390	*1.13*
Dialysis patients	0.132	0.224	0.557	*1.14*	-0.088	0.239	0.714	*0.92*	0.774	0.257	**0.003**	***2.17***	0.150	0.307	0.627	*1.16*	0.099	0.175	0.571	*1.10*
Renal transplant recipients	0.752	0.275	**0.007**	***2.12***	0.751	0.289	**0.010**	***2.12***	0.541	0.300	0.073	*1.72*	0.076	0.428	0.859	*1.08*	0.699	0.222	**0.002**	***2.01***
Infectious diseases	0.301	0.266	0.259	*1.35*	0.934	0.278	**0.001**	***2.54***	0.895	0.261	**0.001**	***2.45***	0.814	0.302	**0.008**	***2.26***	0.618	0.166	**<.001**	***1.86***
Publication year																				
<2000 (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
2000 to <2005	0.562	0.290	0.055	*1.75*	0.453	0.305	0.139	*1.57*	-0.180	0.33	0.582	*0.84*	-0.357	0.385	0.355	*0.70*	0.328	0.213	0.126	*1.39*
2005 to <2010	0.352	0.295	0.234	*1.42*	0.568	0.309	0.069	*1.76*	-0.327	0.330	0.323	*0.72*	-0.630	0.389	0.108	*0.53*	0.238	0.216	0.272	*1.27*
≥2010	0.453	0.296	0.128	*1.57*	0.687	0.311	**0.029**	***1.99***	0.015	0.332	0.965	*1.01*	-0.227	0.392	0.563	*0.80*	0.398	0.217	0.069	*1.49*
Gender – male†	0.518	0.290	0.076	*1.68*	0.519	0.297	0.083	*1.68*	0.092	0.289	0.751	*1.10*	0.549	0.352	0.121	*1.73*	0.340	0.186	0.069	*1.41*
Age at assessment (yrs.)	-0.026	0.007	**0.001**	***0.97***	-0.0003	0.008	0.967	*1.00*	-0.012	0.007	0.103	*0.99*	-0.019	0.010	**0.050**	***0.98***	-0.017	0.005	**0.001**	***0.98***
Estimated Age at infection (yrs.)	0.023	0.008	**0.005**	***1.02***	0.029	0.008	**<.001**	***1.03***	0.035	0.008	**<.0001**	***1.04***	0.027	0.010	**0.009**	***1.03***	0.026	0.005	**<.0001**	***1.03***
Estimated Duration of infection (yrs.)	-0.065	0.007	**<.0001**	***0.94***	-0.036	0.009	**<.0001**	***0.96***	-0.059	0.008	**<.0001**	***0.94***	-0.058	0.010	**<.0001**	***0.94***	-0.052	0.004	**<.0001**	***0.95***
Injecting drug use†	0.022	0.204	0.913	*1.02*	-0.092	0.207	0.657	*0.91*	-0.180	0.199	0.369	*0.84*	0.500	0.236	**0.036**	***1.65***	-0.003	0.128	0.979	*1.00*
Blood transfusion†	0.417	0.273	0.129	*1.52*	0.284	0.279	0.311	*1.33*	0.551	0.263	**0.038**	*1.73*	0.188	0.321	0.559	*1.21*	0.362	0.169	**0.034**	***1.44***
Elevated ALT†	0.852	0.272	**0.002**	***2.34***	0.074	0.297	0.805	*1.08*	-0.058	0.305	0.851	*0.94*	0.332	0.369	0.370	*1.39*	0.476	0.199	**0.018**	***1.61***
Excess alcohol use†	-0.644	0.267	**0.017**	***0.53***	0.432	0.273	0.117	*1.54*	-0.035	0.261	0.893	*0.97*	0.275	0.305	0.368	*1.32*	-0.066	0.165	0.687	*0.94*
HIV positive†	-0.192	0.809	0.813	*0.83*	0.116	0.815	0.888	*1.12*	-0.365	0.770	0.636	*0.69*	1.052	0.909	0.249	*2.86*	-0.069	0.486	0.888	*0.93*
Genotype-1†	-0.080	0.214	0.708	*0.92*	-0.358	0.215	0.099	*0.70*	-0.626	0.199	**0.002**	***0.53***	-0.935	0.236	**<.001**	***0.39***	-0.317	0.129	**0.015**	***0.73***
Genotype-3†	0.378	0.300	0.210	*1.46*	0.259	0.307	0.401	*1.29*	0.376	0.290	0.198	*1.46*	0.962	0.337	**0.005**	***2.62***	0.367	0.184	**0.048**	***1.44***
White†	0.019	0.197	0.925	*1.02*	0.0004	0.201	0.998	*1.00*	-0.188	0.192	0.330	*0.83*	0.147	0.230	0.523	*1.16*	-0.013	0.124	0.918	*0.99*
Black†	-0.440	0.308	0.155	*0.64*	-0.166	0.316	0.601	*0.85*	-0.485	0.298	0.105	*0.62*	-0.759	0.357	**0.035**	***0.47***	-0.374	0.189	**0.050**	***0.69***
Asian†	-0.569	0.409	0.166	*0.57*	-0.196	0.421	0.643	*0.82*	-0.375	0.404	0.355	*0.69*	0.067	0.464	0.885	*1.07*	-0.321	0.254	0.209	*0.73*

Supplementary Table 8. Linear mixed model-maximum likelihood method. *Natural Log-transformed progression rates. Missing were imputed using mean values. †Proportion. Values in bold indicate statistical significance. Abbreviations: Abbreviations: scFPR: stage-constant annual fibrosis progression rate (assuming constant progression over F0 to F4); β: coefficient; SE: standard error; HCV: hepatitis C virus; HIV: human immunodeficiency virus; RNA: ribonucleic acid; CHC: chronic hepatitis

Supplementary Materials

Database search strategy and search strings

1. MEDLINE

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present
Search date: Jan 02, 2018
Limits: 2007 -Current
Filters: BMJ Clinical Evidence - MEDLINE cohort and case-control filter [undated] [Ovid] from website http://www.york.ac.uk/inst/crd/intertasc/observational.htm

Search Strategy:

#	Searches
1	exp cohort studies/
2	cohort$.tw.
3	controlled clinical trial.pt.
4	epidemiologic methods/
5	limit 4 to yr=1966-1989
6	exp case-control studies/
7	(case$ and control$).tw.
8	or/1-3,5-7
9	exp hepatitis C/
10	Hepacivirus/
11	(("parenterally transmitted " or parenterally-transmitted) adj3 ("non a non b hepatitis" or "hepatitis viral non-a non-b")).ti,ab.
12	("hepatitis c" adj2 chronic).ti,ab.
13	(("hepatitis C" or "hepatitis c" or "hepatitis c-like" or "hepatitis c like") adj3 virus$).ti,ab.
14	(virus$ or hepacivirus$ or HCV or "hepatitis c" or "pt-nanbh").ti,ab.
15	or/9-14
16	exp disease progression/
17	((progression? or exacerbation) adj2 disease).ti,ab.
18	fibrosis/
19	Liver Cirrhosis/
20	(fibros$ or cirrhosis).ti,ab.
21	((fibros$ or cirrhosis) adj2 (liver or hepatic)).ti,ab.
22	or/16-21
23	Prognosis/
24	prognos$.ti,ab.
25	disease-free survival/
26	(survival? adj3 ("disease-free" or "disease freeor progression-free" or "progression free" or "event-free" or "event free")).ti,ab.
27	medical futility/
28	(futil$ adj2 (treatment? or medical)).ti,ab.
29	treatment outcome/
30	(treatment adj2 (efficacy or effectiveness or outcome)).ti,ab.
31	(outcome adj2 rehabilitation).ti,ab.
32	treatment failure/
33	(treatment adj2 failure?).ti,ab.
34	morbidity/
35	morbidit$.ti,ab.
36	mortality/
37	(mortalit$ or death rate?).ti,ab.
38	(mortalit$ adj3 (decline? or determinant? or differential or excess)).ti,ab.
39	("death rate?" adj3 ("age-specific" or "age specific")).ti,ab.
40	((death or "case fatality") adj2 rate?).ti,ab.
41	fatal outcome/
42	(outcome? adj2 fatal).ti,ab.

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43	hospital mortality/
44	(mortalit$ adj3 (hospital or "in-hospital" or inhospital or "in hospital" or "in-house" or "in house")).ti,ab.
45	survival rate/
46	(rate adj3 survival adj3 (mean or rate or cumulative)).ti,ab.
47	(survivorship or (survival adj2 (rates or "times mean"))).ti,ab.
48	or/23-47
49	8 and 15 and 22 and 48

2. EMBASE

Databases searched: Embase Classic+Embase 1947 to 2017 December 29
Search date: January 02, 2018
Limits: 2007-Current
Filters: BMJ Clinical Evidence - EMBASE cohort and case-control filter [undated] [Ovid] from website http://www.york.ac.uk/inst/crd/intertasc/observational.htm

Search Strategy:

#	Searches
1	exp hepatitis C/
2	exp hepatitis C virus/
3	(("parenterally transmitted " or parenterally-transmitted) adj3 ("non a non b hepatitis" or "hepatitis viral non-a non-b")).ti,ab.
4	("hepatitis c" adj2 chronic).ti,ab.
5	(("hepatitis C" or "hepatitis c" or "hepatitis c-like" or "hepatitis c like") adj3 virus$).ti,ab.
6	(hepacivirus$ or HCV or "hepatitis c" or "pt-nanbh").ti,ab.
7	or/1-6
8	exp disease course/
9	((progression? or exacerbation) adj2 disease).ti,ab.
10	liver fibrosis/
11	fibrosis.ti,ab.
12	liver cirrhosis/
13	(fibros$ or cirrhosis).ti,ab.
14	((fibros$ or cirrhosis) adj2 (liver or hepatic)).ti,ab.
15	or/8-14
16	prognosis/
17	prognos$.mp.
18	disease-free survival/
19	(survival? adj3 ("disease-free" or "disease freeor progression-free" or "progression free" or "event-free" or "event free")).ti,ab.
20	(futil$ adj2 (treatment? or medical)).ti,ab.
21	treatment outcome/
22	(treatment adj2 (efficacy or effectiveness or outcome)).ti,ab.
23	(outcome adj2 rehabilitation).ti,ab.
24	treatment failure/
25	(treatment adj2 failure?).ti,ab.
26	morbidity/
27	morbidit$.ti,ab.
28	mortality/
29	(mortalit$ or death rate?).ti,ab.
30	(mortalit$ adj3 (decline? or determinant? or differential or excess)).ti,ab.
31	(death rate? adj3 ("age-specific" or "age specific")).ti,ab.
32	fatality/
33	(outcome? adj2 fatal).ti,ab.
34	(mortalit$ adj3 (hospital or "in-hospital" or inhospital or "in hospital" or "in-house" or "in house")).ti,ab.
35	survival rate/
36	(rate adj3 survival adj3 (mean or rate or cumulative)).ti,ab.
37	(survivorship or (survival adj2 (rates or "times mean"))).ti,ab.

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38	or/16-37
39	exp cohort analysis/
40	exp longitudinal study/
41	exp prospective study/
42	exp follow up/
43	cohort$.tw.
44	exp case control study/
45	(case$ and control$).tw.
46	or/39-45
47	7 and 15 and 38 and 46

PUBMED

Databases searched: PubMed

Limits: Publication date from 2007/01/01 to 2018/01/02

Filters: BMJ Clinical Evidence - EMBASE cohort and case-control filter [undated] [Ovid translated into PubMed] from website http://www.york.ac.uk/inst/crd/intertasc/observational.htm

Search Strategy:

((cohort studies[mesh]) OR (cohort$[Title]) OR (epidemiologic methods[mesh:noexp]) OR (case-control studies[mesh]) OR ((case$ AND control$) AND Title) OR (limit AND (epidemiologic methods[mesh:noexp]) AND to yr=1966-1989)) **AND** ((hepatitis C[mesh]) OR (Hepacivirus[mesh:noexp]) OR ((("parenterally transmitted"[tiab] OR parenterally-transmitted[tiab]) AND ("non a non b hepatitis"[tiab] OR "hepatitis viral non-a non-b"[tiab])) OR (("hepatitis c"[tiab] AND chronic[tiab])) OR ((("hepatitis C"[tiab] OR "hepatitis c"[tiab] OR "hepatitis c-like"[tiab] OR "hepatitis c like"[tiab]) AND virus$[tiab])) OR ((virus$[tiab] OR hepacivirus$[tiab] OR HCV[tiab] OR "hepatitis c"[tiab] OR "pt-nanbh"[tiab]))) **AND** ((disease progression[mesh]) OR (((progression*[tiab] OR exacerbation[tiab]) AND disease[tiab])) OR (fibrosis[mesh:noexp]) OR (Liver Cirrhosis[mesh:noexp]) OR ((fibros$[tiab] OR cirrhosis[tiab])) OR (((fibros$[tiab] OR cirrhosis[tiab]) AND (liver[tiab] OR hepatic[tiab])))) **AND** ((Prognosis[mesh:noexp]) OR (prognos$[tiab]) OR (disease-free survival[mesh:noexp]) OR ((survival*[tiab] AND ("disease-free"[tiab] OR "disease free"[tiab] OR "progression-free"[tiab] OR "progression free"[tiab] OR "event-free"[tiab] OR "event free"[tiab]))) OR (medical futility[mesh:noexp]) OR ((futil$[tiab] AND (treatment*[tiab] OR medical[tiab]))) OR (treatment outcome[mesh:noexp]) OR ((treatment[tiab] AND (efficacy[tiab] OR effectiveness[tiab] OR outcome[tiab]))) OR ((outcome[tiab] AND rehabilitation[tiab])) OR (treatment failure[mesh:noexp]) OR ((treatment[tiab] AND failure*[tiab])) OR (morbidity[mesh:noexp]) OR (morbidit$[tiab]) OR (mortality[mesh:noexp]) OR ((mortalit$[tiab] OR death rate*[tiab])) OR ((mortalit$[tiab] AND (decline*[tiab] OR determinant*[tiab] OR differential[tiab] OR excess[tiab]))) OR (("death rate*"[tiab] AND ("age-specific"[tiab] OR "age specific"[tiab]))) OR (((death[tiab] OR "case fatality"[tiab]) AND rate*[tiab])) OR (fatal outcome[mesh:noexp]) OR ((outcome*[tiab] AND fatal[tiab])) OR (hospital mortality[mesh:noexp]) OR ((mortalit$[tiab] AND (hospital[tiab] OR "in-hospital"[tiab] OR inhospital[tiab] OR "in hospital"[tiab] OR "in-house"[tiab] OR "in house"[tiab]))) OR (survival rate[mesh:noexp]) OR ((rate[tiab] AND survival[tiab] AND (mean[tiab] OR rate[tiab] OR cumulative[tiab]))) OR ((survivORship[tiab] OR (survival[tiab] AND (rates[tiab] OR "times mean"[tiab])))))

Supplementary Materials

List of extracted data items

Previously identified data items were abstracted in duplicate by two independent reviewers using piloted abstraction sheets in excel. Study authors were not contacted to obtain missing data. For non-English studies, native speakers were contacted for help with full-text review and data extraction process. Abstract were not included in the current analysis as these records do not report information necessary for estimating prognosis (i.e. duration of infection).

1. **Study related factors:**
   - Study design (i.e. cross-sectional/retrospective, retrospective-prospective, prospective)
   - Study setting (i.e. clinical, non-clinical)
   - Study population (i.e. blood donor, female cohort, dialysis patient, IDUs, community, pediatric, post-transfusion, renal transplant recipients)
   - Sample size
   - Country
2. **Host-related factors:**
   - Gender (n, % male)
   - Mean age at assessment of liver disease (years)
   - Mean age at HCV acquisition [where unavailable, data were calculated by taking the difference between mean age at assessment of liver disease and the mean duration of HCV infection] (years)
   - Mean estimated duration of HCV infection (years)
   - Mode of HCV acquisition (n, %: IDU, blood transfusion, sporadic)
   - Excess alcohol consumption [as defined in study] (n, %)
   - Mean body mass index (BMI) (kg/m^2)
   - History of diabetes mellitus (n, %)
   - Coinfection with HBV (n, % HBsAg positive)
   - Coinfection with HIV (n, %)
3. **Virus related factors:**
   - HCV genotype (n, %: G1, G2, G3, G4, other)
   - HCV RNA positivity (n, %)
   - HCV RNA viral load (IU/ml)
4. **Liver-related factors**
   - Elevated ALT levels (n, %)
   - Mean ALT (IU/L)
   - Presence of hepatic steatosis (n, %)
   - Method of fibrosis assessment (e.g. LB, TE, combination LB and non-invasive)
   - Method of fibrosis scoring (e.g. METAIR, Ishak, or cutoffs for non-invasive tests)
   - Fibrosis stage distributions at latest available follow-up point (n, %: F0 to F4) [where data were reported as composite (i.e., F0/F1) a 50:50 distributions was applied to the 2 stages. Stage distribution was not performed if more than two stages were reported in composite]
   - Liver biopsy length (mm)
   - Clinical or histological diagnosis of cirrhosis (n. %)
   - Mean histological activity index (HAI) Inflammatory score

Note on missing data: Age at infection, for studies that did not report this, was imputed by taking the difference between age at assessment and the duration of infection. For studies that report composite fibrosis stages (e.g., F0/F1), data were distributed 50:50 across F0 and F1**.** Stage distribution was not performed when more than two stages were reported collectively (e.g., F0/F1/F2).

Supplementary Materials

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MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	5-6
2	Hypothesis statement	[Descriptive]
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6 [Natural history of CHC]
5	Type of study designs used	6
6	Study population	6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	6-7
8	Search strategy, including time period included in the synthesis and key words	6-7, 51-53 [Supplemental methods]
9	Effort to include all available studies, including contact with authors	6-7, 51-53 [Supplemental methods]
10	Databases and registries searched	6-7, 51-53 [Supplemental methods]
11	Search software used, name and version, including special features used (eg, explosion)	6-7, 51-53 [Supplemental methods]
12	Use of hand searching (eg, reference lists of obtained articles)	6-7
13	List of citations located and those excluded, including justification	44-46 [Supplemental methods]
14	Method of addressing articles published in languages other than English	7,54 [Supplemental methods]
15	Method of handling abstracts and unpublished studies	7,54 [Supplemental methods]
16	Description of any contact with authors	7,54 [Supplemental methods]
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-8, 25 [Table1]
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7,27,54 [TableS1]
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	7,27,54 [TableS1]
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	8
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	8-9

22	Assessment of heterogeneity	8-9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8-9
24	Provision of appropriate tables and graphics	23 [Fig1]
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	26 [FigS1]
26	Table giving descriptive information for each study included	29-43 [TableS3, TableS4]
27	Results of sensitivity testing (eg, subgroup analysis)	20,24,48 [Table2, Fig2, TableS6]
28	Indication of statistical uncertainty of findings	20-21 [Table2, Table 3]

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	8-9, 13-15
30	Justification for exclusion (eg, exclusion of non-English language citations)	15
31	Assessment of quality of included studies	13,15
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	14-15
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	15
34	Guidelines for future research	15
35	Disclosure of funding source	1

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Estimation of fibrosis progression rates for chronic hepatitis C: a systematic review and meta-analysis update

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Estimation of fibrosis progression rates for chronic hepatitis C: a systematic review and meta-analysis update

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Abbreviations

HCV	hepatitis C virus
CHC	chronic Hepatitis C
FPR	fibrosis progression rate
BMI	body mass index
HBV	hepatitis B virus
HIV	human immunodeficiency virus
MMLE	markov maximum likelihood estimation
ALT	alanine aminotransferase
RNA	ribonucleic acid
CI	confidence interval
IDU	injection drug user
RR	relative risk
scFPR	stage-constant fibrosis progression rate

Abstract

Objectives: Mathematical models are increasingly important in planning for the upcoming chronic hepatitis C (CHC) elimination efforts. Such models require reliable natural history inputs to make accurate predictions on health and economic outcomes. Yet, HCV disease progression is known to vary widely in the literature and published inputs are currently outdated. The objectives of this study were to obtain updated estimates of fibrosis progression rates (FPRs) in treatment-naïve CHC patients and to explore sources of heterogeneity.

Design: A systematic review was conducted using Ovid-MEDLINE, Ovid-EMBASE, and PubMed databases (January 1990 – January 2018) to identify observational studies of hepatic fibrosis in treatment-naïve CHC patients.

Outcomes: Stage-constant FPRs were estimated for each study given the reported fibrosis scores and duration of infection. Stage-specific FPRs (i.e., F0→F1; F1→F2; F2→F3; F3→F4) were estimated using Markov Maximum Likelihood estimation. Estimates were pooled using random-effects meta-analysis and heterogeneity was evaluated by stratification and random-effects meta-regression.

Results: The review identified 111 studies involving 131 groups of patients (N=42,693). The pooled stage-constant FPR was 0.094 (95%CI, 0.088-0.100), stage-specific FPRs were F0→F1: 0.107 (95%CI, 0.097-0.118); F1→F2: 0.082 (95%CI, 0.074-0.091); F2→F3: 0.117 (95%CI, 0.107-0.129); F3→F4: 0.116 (95%CI, 0.104-0.131). Stratified analysis revealed substantial variation in progression by study population. Meta-regression indicated associations between progression and infection age, duration, source, viral genotype and study population. Findings indicate that FPRs display substantial heterogeneity across study populations and pooled values from more homogenous subpopulations should be considered when estimating prognosis.

Conclusions: This large meta-analysis presents updated prognostic estimates for CHC derived from newer studies using better diagnostic methods and improves estimates for important patient populations in terms of clinical policy (e.g., injection drug users, non-clinical populations, liver clinic patients) and should be a valuable resource for patients, clinicians and clinical policy makers.

Strengths and limitations of this study

- Our updated meta-analysis is now the largest review of HCV prognosis including English and non-English language observational studies.
- We use Markov maximum likelihood estimation method, which does not rely on the assumption of a linear disease progression to obtain detailed stage-specific estimates of fibrosis progression.
- Further, we restrict our meta-analysis to newer studies using better diagnostic methods compared to earlier reviews; and we present more precise prognostic estimates for important CHC subpopulations in terms of clinical policy (i.e., injection drug users, blood transfusion cohorts, liver clinic patients and non-clinical populations).
- However, findings indicate that FPRs display substantial heterogeneity across study populations and pooled values from more homogenous subpopulations should be considered when estimating prognosis.

Introduction

An estimated ~1% of the world's population is infected with the Hepatitis C virus (HCV) [1,2]. Chronic HCV (CHC) eventually leads to fibrosis, cirrhosis, advanced liver disease, and death [1,3,4]. The level of CHC-related hepatic fibrosis is typically detected through histology using the METAVIR scoring system with scores ranging from F0 indicating no fibrosis to F4 indicating cirrhosis. Published estimates of CHC prognosis has shown large variability in the rate of fibrosis progression across these stages [5–8].

Fortunately, HCV treatment has been revolutionized by highly effective therapies making elimination a plausible objective. Recently, the World Health Organization (WHO) launched a global strategy to this end, targeting a 90% reduction in new infections, a 65% reduction in liver-related death, a diagnosis rate of 90% and a treatment rate of 80% by 2030. This will necessitate radical expansions in prevention, screening and linkage to care [9].

However, a key challenge to the development of national elimination strategies has been the lack of reliable estimates of local disease burden, HCV prevalence and the prevalence of the undiagnosed population [9]. Currently, the only way to estimate such unknown parameters involves mathematical modeling. For this reason, WHO has been assisting countries through expert consultation and modelling initiatives [9]. Mathematical models are also increasingly important for estimating the health and economic consequences of scaling-up screening and treatment programs. However, these models require reliable natural history inputs to make accurate predictions [10,11]. Yet, HCV disease progression is known to vary widely in the literature and published natural history inputs are currently outdated [5–8].

In general, the variability in HCV disease progression has been attributed to differences in the study population (e.g., liver clinic, blood donors, injection drug users); differences due to study setting (i.e., clinical vs. non-clinical); differences among study subjects with respect to clinical risk factors for disease progression [12–14]; as well as to variation in the methods used for calculating fibrosis progression rates (FPRs) [15].

The established clinical risk factors for rapid progression of hepatic fibrosis include older age, male gender, excessive alcohol use, high body mass index (BMI), and HBV or HIV coinfection [12–14].

However, more recent studies have indicated race/ethnicity and viral genotype as possible risk factors as well [16–20]. Studies have also suggested that patients identified in clinical settings display a more rapid progression compared to those identified in non-clinical settings, for example by screening programs [5].

In terms of methodological variability, studies generally estimate progression using two methods: a direct method involving serial biopsies, and an indirect method involving a single biopsy and the estimated duration of infection [15]. Multiple biopsies are less common and often involve patients who need to be monitored closely for rapid progression; while, the more common indirect method assumes a constant progression rate from the time of infection despite evidence indicating variability between stages [5,21,22].

To account for stage-specific variation in progression, Yi *et al* [22] have proposed the Markov Maximum Likelihood Estimation (MMLE) method, which can estimate accurate stage-specific FPRs from observational studies where only a single biopsy and the estimated duration of infection are available. This has improved the external validity and accuracy of stage-specific progression estimates by allowing much larger numbers of single biopsy studies to inform HCV prognosis [22].

A previous systematic review from our group has estimated FPRs using this method [5]. This study has been widely-used in pharmacoeconomic evaluations. However, since its publication, a decade ago, new prognostic studies have become available, highlighting additional sources of variability (i.e., viral genotype, race/ethnicity) that merit further investigation [16–19,23,24].

Given the availability of new research and the importance of natural history estimates particularly for informing forthcoming elimination policies, the objectives of this study were: (1) to refine progression estimates through an updated systematic review of observational studies examining hepatic fibrosis in treatment naïve HCV-infected individuals and (2) to further explore additional sources of heterogeneity.

Materials and methods

Data sources

A systematic literature search was conducted using Ovid MEDLINE, Ovid EMBASE, and PubMed databases without language restriction by an experienced medical librarian (JB) [original: January 1990-

August 2007; update: January 2007-January 2018]. Additionally, the search was supplemented by citation searches and by reviewing references of relevant studies. Search strings for each database are provided in **Supplemental Methods.**

Study selection

Records were imported to EndNote X7.7.1 (Thomson Reuters, New York City, NY, USA). After duplicate removal, potentially relevant studies were screened against eligibility criteria by two independent reviewers. Disagreements were resolved through discussion.

Studies were included if they satisfied the following criteria: (1) CHC defined as the presence of anti-HCV antibody detected by second or third generation enzyme-linked immunosorbent assay and at least one of the following: HCV RNA detected by polymerase chain reaction, recombinant immunoblot assay, elevated alanine aminotransferase (ALT), or liver biopsy; (2) full-length peer-reviewed original observational study; and (3) no HCV treatment prior to biopsy. Studies involving fewer than 20 cases, post-liver transplant patients and those where FPRs could not be calculated were excluded. Multiple reports from the same study were identified by comparing author, year, and sample size. The report with the most complete information was preferred, if equivalent, then the most recent publication was included.

Data extraction

Study, host, viral and liver-disease related information were extracted in duplicate by two independent reviewers using piloted forms. For non-English studies, native speakers were contacted for help with full-text review and data extraction processes. A complete list of abstracted data items and all abstracted data are provided in the **Supplement**. Studies that reported results in subgroups, which may influence disease progression were extracted separately.

Age at HCV acquisition, for studies that did not report this information, was imputed by taking the difference between age at assessment and the estimated duration of infection. For some studies that report composite fibrosis stages (e.g., F0/F1), data were distributed 50:50 across F0 and F1. Stage distribution was not performed when more than two stages were reported collectively (e.g., F0/F1/F2).

Definitions used by reviewers and criteria used to convert histological and non-invasive scores to the METAVIR system are provided in **S1 and S2 Tables** respectively.

Study quality

Because the included studies vary widely by study design, population and setting, and since the study outcomes (i.e., FPRs) were generated using the MMLE method (given the duration of infection and the fibrosis scores reported in each study), rather than being directly extracted from the included studies, instead of applying a generic quality appraisal tool, we addressed issues that may bias outcome measurement and the accuracy of FPR estimation more directly**.** To improve the accuracy of case ascertainment, the updated meta-analysis was restricted to newer studies where all participants had confirmatory RNA testing for CHC. Further, studies were stratified by two independent reviewers by the mode of infection, which can influence the estimation of the duration of infection, as well as by study design, setting, and population to address issues around representativeness/generalisability of findings. The categories were based on the criteria described in **Table S2**. Finally, other clinical factors such as excess alcohol use and HIV or HBV coinfection among study subjects, which may impact outcomes were adjusted for using meta-regression analyses.

Estimation of fibrosis progression rates

Two methods were used to estimate the annual FPRs for each included study: (1) The stage-constant FPR was estimated by dividing the total number of transitions in METAVIR units by the person-years of HCV infection; (2) The stage-specific FPRs (i.e., F0→1, F1→2, F2→3 and F3→F4) were estimated using the MMLE method [22].

Data synthesis

Identified groups were stratified by methodological and clinical subgroups. Estimates were pooled by random-effects meta-analyses. Time-to-cirrhosis was determined using the pooled stage-specific progression rates (α_s) [5,22]:

$$Time - to - Cirrhosis = \left(\frac{1}{\alpha_{01}} + \frac{1}{\alpha_{12}} + \frac{1}{\alpha_{23}} + \frac{1}{\alpha_{34}}\right)$$

Finally, the pooled FPRs and their 95% confidence intervals (CI) were used to estimate the mean cumulative probability of cirrhosis up to 40 years after HCV exposure for clinically important subpopulations.

Heterogeneity

For all estimates, publication bias, small study effects and heterogeneity were assessed by visual inspection of funnel plots of the natural log of FPRs against inverse variance. A statistical test for funnel plot asymmetry was not performed due to presence of significant heterogeneity (**S1 Fig)** [25,26]. Heterogeneity was quantified using the I^2 statistic, with values of 25% and 75% indicating low and high heterogeneity [27]. Previously identified sources of heterogeneity (e.g., study-related, methodological, clinical and viral) were explored through stratification and random-effects meta-regression analyses using a linear mixed model – maximum likelihood method weighted by a multiplicative variance adjustment factor [5,12–14,18]. Missing values were imputed using the mean values. The natural log of FPRs were used as the dependent variable.

Statistical analysis

Statistical analysis was conducted using SAS (SAS Inc, Cary, NC, USA) and PROC MIXED and PROC MIXED ML procedures were used for all meta-analyses and meta-regression analyses. The plots were generated using RStudio v1.1.383 (RStudio, Boston, MA, USA). A two-sided significance level of 0.05 was used to indicate significance for hypothesis tests.

Results

Study selection

The current study is an update of a previous review covering the period from January 1990 to August 2007 [5]. The updated literature search (January 2007- January 2018) identified a total 10,440 records **(Fig 1)**. Following duplicate removal, 7,193 abstracts were screened, and 1,304 records were included for full-text review. Overall, the update identified 45 new studies reporting on 60 new patient groups (24,689 HCV infected subjects) resulting in total of 140 studies and 171 groups of patients (57,810 subjects) in

combination with the earlier review. Group-level summary of study and participant characteristics are provided in **S3 and S4 Tables** respectively.

However, the updated meta-analysis was restricted to newer studies where all participants had HCV RNA testing. After elimination of 40 study groups where RNA status was either missing or unclear, the updated meta-analysis included 111 studies reporting on 131 groups of patients (42,693 subjects and 723,058 person-years of follow-up time). The study characteristics of the 40 study groups excluded from the meta-analysis are described in **S5 Table** in the **Supplement**.

Study characteristics

The study characteristics of the 131 groups included in the meta-analysis are summarized in **Table 1.** A majority, 84% (N=110), of the included groups were assessed in a clinical setting (vs. non-clinical). Compared to the original review, the update identified relatively more patients evaluated in a non-clinical setting [12% (N=3,068) of original vs. 31% (N=5,392) of new subjects]. In terms of study design, a majority, 68% (N=88) used a cross-sectional/retrospective vs. a retrospective-prospective study design. Majority of study groups (124 out of 131) assessed hepatic fibrosis using only histology; only 7 performed a non-invasive assessment of hepatic fibrosis (6 used LSM and 1 used a combination of invasive and non-invasive methods).

Regarding the patient populations, liver clinic patients were the most frequently studied group (69%). In total, there were 91 groups of liver clinic patients; 10 of injection drug users (IDUs); 6 of dialysis patients; 5 of females, 4 community, renal transplant recipients and infectious diseases patients; 3 of blood donor groups; and 2 of pediatric and post-transfusion groups (**Table 1**). Furthermore, the update identified a total of 10 evaluations of genotype-1, 3 of genotype-3 and 1 each of genotypes 2 and 4 infected groups.

Clinical characteristics of study subjects

The clinical characteristics of subjects are summarized in **S6 Table**. The majority of the subjects were male (62%) and white (69%). The mean age at assessment of liver fibrosis was 44 years, the mean age at infection was 26 years and the mean duration of infection of 18 years. The average prevalence of excess alcohol use was 20%. Injection drug use accounted for 43% and blood transfusion for 26% of

infections. Cirrhosis was present in 12%. The majority, of the subjects (76%) had an elevated ALT. The mean ALT of all subjects was 88IU/L. In terms of viral genotype, the average prevalence of genotype-1 was 56%, genotype-3 was 18%. On average, 2% of subjects were coinfected with HIV and 0.4% with HBV.

Overall fibrosis progression rates

The pooled stage-constant FPR was 0.094 (95%CI, 0.088-0.100) METAVIR units per year (**Table 2**). The stage-specific FPR estimates were generally lower for transitioning between F0→F1 (0.107; 95%CI, 0.097-0.118) and F1→F2 (0.082; 95%CI, 0.074-0.091); relative to F2→F3 (0.117; 95%CI, 0.107-0.129) and F3→F4 (0.116; 95%CI, 0.104-0.131). Overall, the estimated time-to-cirrhosis was 39 years. The I^2-statistic indicated a high level of heterogeneity which were relatively more pronounced at earlier stages. The pooled FPRs stratified by study update are provided in **S7 Table**. Forrest plots of the pooled stage-specific FPRs are provided in figures **S2-S5 Fig** in the **Supplement**.

Stratification by study setting and design

Time-to-cirrhosis estimates indicated a faster progression to cirrhosis in groups initially identified in a clinical vs. non-clinical setting (37 vs. 47 years) (**Table 2**). In terms of study design, there was only a small difference in progression among cross-sectional/retrospective vs. retrospective-prospective design (38 vs. 41 years), which was lost following adjustment for covariates (**S8 Table**). The cumulative probability of cirrhosis by study setting is presented in **Fig 2**.

Stratification by study population

Time-to-cirrhosis estimates indicated a relatively slower progression to cirrhosis for the female (74 years), blood donor (63 years), pediatric (45 years), and post transfusion cohorts (44 years) and a faster progression for infectious diseases (19 years), renal transplant (24 years), dialysis (35 years), community (35 years) and IDU (37 years) populations relative to liver clinic populations (40 years) (**Table 2**).

In general, simple stratification by study population was able to explain heterogeneity in estimates primarily for the later stages of disease. However, a high level of heterogeneity persisted for liver clinic,

IDU and community groups. The unadjusted cumulative probability of cirrhosis for different study populations are displayed in **Fig 2**.

Based on time-to-cirrhosis estimates derived from covariate-adjusted FPRs, female (52 years), blood donor (55 years) and post-transfusion (44 years) groups maintained a relatively slower progression, while pediatric groups (36 years) displayed a slightly faster progression relative to liver clinic populations (38 years) (**S8 Table)**. Infectious diseases (34 years) and community (33 years) groups maintained a relatively faster progression following adjustments, while the covariate-adjusted progression was somewhat comparatively slower for dialysis patients (47 years), renal transplant (39 years) and IDUs (40 years).

Stratification by publication year

Based on unadjusted time-to-cirrhosis estimates, earlier studies (< year 2000) indicated a slower progression to cirrhosis (49 years) vs. studies published after 2000 (**Table 2)**. This was also apparent following covariate adjustment (**S8 Table**).

Stratification by age and duration of infection

In terms of age, groups with a younger mean age at assessment (<40 years) displayed a faster progression to cirrhosis (33 years) vs. an older age (≥40) (40 years) (**Table 2**). While groups with an older age at infection (≥ 30 years) displayed a more rapid progression (20-28 years) relative to a younger age (< 30 years) (42-45 years). Fibrosis also progressed faster (17 years) in groups with a shorter duration of infection (< 10 years).

Stratification by viral genotype

Regarding viral genotype, groups infected with viral genotype-1 displayed a much slower progression to cirrhosis vs. genotype-3 (59 vs. 30 years) (**Table 2**). Slower progression for genotype-1 vs. genotype-3 groups remained following covariate adjustments (43 vs. 34 years) (**S8 Table)**. In the stratified analysis, genoytpe-3 groups exhibited considerably less heterogeneity vs. genotype-1. The unadjusted cumulative probability of cirrhosis for genotypes 1 and 3 are displayed in **Fig 2**.

Univariate analysis

In the univariate analyses, most clinical covariates displayed an association with at least one progression estimate except for HIV coinfection, male sex, white and Asian race (**S9 Table**). For more advanced stages of disease, genotype-1 was associated with a slower progression to advanced fibrosis (F2→F3; RR=0.53) and to cirrhosis (F3→F4; RR=0.39); while, genotype-3 was associated with faster progression to cirrhosis (RR=2.62). Additionally, injection drug related infections displayed faster (RR=1.65) and black race slower progression (RR=0.47) to cirrhosis.

Regarding study-related factors, studies conducted in a non-clinical setting (vs. clinical) indicated a slower progression in the earlier stages of disease (RR=0.68-0.75). In terms of study population, relative to liver clinic patients, IDUs (RR=1.72) and infectious diseases groups (RR=2.26), displayed a faster and females (RR=0.46) displayed a slower progression to cirrhosis. For earlier stages, dialysis, renal transplant and infectious diseases populations all exhibited a faster (RR=2.12-2.54) and females again displayed a slower progression (RR=0.45). Many covariates (e.g., infectious diseases, females, genotype 3) were also associated with the overall progression (scFPR).

Multivariable analysis

After adjusting for multiple covariates (**Table 3**), the duration of infection remained independently associated with slower progression for all FPRs (RR=0.94-0.97). Age at infection was also independently associated with faster progression between F1→F2 (RR=1.03) and with overall progression (scFPR; RR=1.01). Similarly, blood transfusion-related infection displayed faster progression from F0→F1 (RR=2.37) and in overall progression (scFPR; RR=1.63). Regarding viral genotype, following adjustment for covariates, genotype-1 was significantly associated with a slower progression between F2→F3 (RR=0.58) and faster progression from F0→F1 (RR=1.61). No significant association was observed for viral genotype-3 or for ethnicity. In terms of study-related factors, only dialysis populations maintained a significant association after covariate-adjustment, exhibiting a slower progression vs. liver clinic patients, at early stages (F1→F2; RR=0.58). Based on the adjusted-R^2, covariates explained ~38-56% of the heterogeneity in the stage-specific FPR estimates and 87% in the stage-constant estimate.

Discussion

Our large systematic review of HCV natural history presents updated and refined estimates of CHC-related hepatic fibrosis progression in treatment naïve patients. Overall, the updated estimates were generally consistent with previous studies and indicated an average time-to-cirrhosis of ~39 years [5,14,28]. However, the current study found a slightly slower progression compared to our previous analysis, especially at the earliest stage of fibrosis [5]. This is possibly because the updated review included more studies where patients were identified through screening efforts in non-clinical settings, and thus involved less symptomatic patients when compared to the original study.

In general, the current update improves upon our previous analysis by focusing on more recent studies where CHC was confirmed by better diagnostic methods and by incorporating substantially more subjects identified in a non-clinical setting (8,460 vs. 3,068) and more IDU populations (5,132 vs. 670) thereby providing more precise estimates of progression for these important subpopulations. Further, we identified study population as an important source of heterogeneity indicating that population-specific estimates should be considered when estimating prognosis. With respect to the IDU population, based on the 10 groups identified, we found a faster average time-to-cirrhosis for this population (37 years), when compared to our earlier estimate (40 years), and to a previous review, which used similar methods (46 years) [29]. Following covariate adjustments, the progression was slightly slower (40 years); this could be due to the inclusion of more genotype-3 infected individuals in the present study.

In our updated analysis we also further explored the effects of viral genotype and race/ethnicity on prognosis. Univariate analyses identified genotype-3 as a predictor of faster and genotype-1 a predictor of slower progression from advanced fibrosis to cirrhosis. Similarly, a previous meta-analysis of stage-constant FPR also found a faster progression for genotype-3 vs non-3 groups [18]. Due to the small number of studies a meta-regression could not be used to explore confounders in that study. In our large meta-regression, genotype-1 displayed a faster progression at the earliest but a slower progression at more advanced stages of fibrosis. Similarly, univariate analysis also indicated a slower progression from significant fibrosis to cirrhosis for black race and female populations in agreement with previous studies; [20,24,30] although these relationships were lost upon covariate adjustment.

To help describe the differences in disease progression across the different groups, our updated analysis used the covariate-adjusted stage-specific fibrosis progression rates to estimate the average expected time-to-cirrhosis for each group. After adjustment for confounders, we found that time-to-cirrhosis was 43 years for genotype-1 vs. 34 years for genotype-3 groups. In general, adjusted progressions were slower for the blood donors (55 years), females (52 years), Black patients (46 years) and generally faster for IDUs (40 years), infectious diseases units and community patients (~34 years) and Asian populations (29 years).

Our study is limited in several ways. We excluded reports where the data on infection duration were not available. Thus, the results may not be generalizable to individuals with an unknown source of infection. Moreover, estimates based on self-report such as, the duration of infection, alcohol and drug use, may suffer from recall bias. Studies in IDUs suggest that there may exist a median lag of ~3 years between the first year of drug use and HCV-infection [17,31]. Therefore, the accuracy of the estimates of infection duration may vary by the mode of infection [32], resulting in a possible underestimation of FPRs for IDUs. Additionally, alcohol use tends to be inconsistently reported. Finally, aggregated analyses may suffer from ecological fallacy [33]. It is also important to note that although newer non-invasive methods are replacing biopsy, non-invasive prognosis currently remains limited making biopsy-based stage-specific estimates the most suitable method for representing the natural history of HCV at the current time [34].

Finally, our analyses identified substantial heterogeneity, especially among earlier vs. later stages of fibrosis. This is not surprising as published estimates are known to vary extensively. While we have explained some of this variation, it is possible that some heterogeneity is also related to sampling variability associated with biopsies, though, non-invasive estimates also demonstrate considerable variability [34]. Other sources of variation may include obesity, steatosis, insulin resistance or genetic factors that can moderate fibrogenesis, which remain largely unreported in the literature [35–39]. Furthermore, I^2-statistic, which measures the extent of variation due to heterogeneity vs. sampling error may be inflated when study sizes are large or sampling error is low as in our case [40].

Our study also has significant strengths: (1) it is the largest meta-analysis of HCV prognosis including English and non-English language studies; (2) it uses the MMLE method to obtain detailed stage-specific

estimates of HCV prognosis in treatment naïve patients, a method that does not rely on the assumption of linear disease progression; (3) compared to our original study, the current update improves the precision of prognostic estimates for important patient groups in terms of clinical-policy (i.e., asymptomatic patients identified in non-clinical settings through screening efforts, injection drug users, blood transfusion populations, liver clinic patients); (4) our update was also restricted to more recent studies where CHC is identified using better diagnostic tests; (5) further, the large numbers of included studies has allowed for us to explain ~38-87% of the apparent heterogeneity in progression; and finally, (6) we present natural history data that can be easily applied to mathematical models for estimating HCV prevalence, disease burden, resource utilization, budget impact and cost-effectiveness, all of which will be necessary for planning appropriate elimination programs in the near future. Furthermore, given the level of heterogeneity identified across studies, our updated analysis suggests that pooled progression estimates from more homogenous subpopulations should be considered when estimating prognosis in policy models.

In Conclusion, the accurate estimation of HCV disease progression remains important in the era of HCV elimination particularly due to existing policy question around elimination strategies, which necessitate modeling-based methods to help inform policy. The current study is now the largest and most detailed review of HCV prognosis, which presents more precise prognostic estimates for important subpopulations in terms of clinical policy and should be a valuable resource for clinicians, patients and particularly clinical policy makers.

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Table 1: Summary of subgroups included in the meta-analysis

	Updated Review (1990-2018)		Original Review (1990-2007)		New Groups (2007-2018)	
	N	**SS**	**N**	**SS**	**N**	**SS**
All groups	131	42,693	81	25,492	50	17,201
Study setting						
Clinical	110	34,233	70	22,424	40	11,809
Non-clinical	21	8,460	11	3,068	10	5,392
Study design						
Cross-sectional/Retrospective	88	29,088	72	22,921	16	6,167
Retrospective-Prospective	43	13,605	9	2,571	34	11,034
Study population						
Females	5	1,420	4	1,400	1	20
Blood donors	3	408	2	223	1	185
Pediatric patients	2	223	0	.	2	223
Post transfusion	2	509	1	469	1	40
Liver clinic	91	32,524	61	21,338	30	11,186
Injection drug users	10	5,132	4	670	6	4,462
Community	4	1,451	3	1,044	1	407
Dialysis patients	6	408	3	191	3	217
Renal transplant	4	179	3	157	1	22
Infectious diseases	4	439	0	.	4	439
Publication year						
<2000	4	629	4	629	0	0
2000 to <2005	56	16,460	54	16,309	2	151
2005 to<2010	37	12,041	23	8,554	14	3,487
≥2010	34	13,563	0	.	34	13,563
Age at assessment						
Age<40	23	5,540	13	2,166	10	3,374
Age≥ 40	108	37,153	68	23,326	40	13,827
Estimated age at Infection						
<20 years	11	2,318	4	662	7	1,656
30 to <40 years	95	35,926	64	21,576	31	14,350
20 to <30 years	19	3,864	13	3,254	6	610
≥40 years	6	585	0	.	6	585
Estimated duration of infection						
<10 years	8	834	2	212	6	622
10 to <20 years	71	21,949	50	13,800	21	8,149
≥ 20 years	52	19,910	29	11,480	23	8,430
HCV genotype						
Genotype 1	10	3,000	5	1,854	5	1,146
Genotype 2	1	90	0	.	1	90
Genotype 3	3	1,426	0	.	3	1,426
Genotype 4	1	117	0	.	1	117

Table 1. Summary of subgroups included in the meta-analysis. The meta-analysis was restricted to 131 study groups (81 from the original review and 50 new groups) where CHC was confirmed by HCV RNA testing in all subjects. *Abbreviations: N: number of groups included in the meta-analysis; SS: total sample size in each group.; CHC: chronic hepatitis C.*

Table 2: Random-effects meta-analysis of hepatic fibrosis progression rates stratified by CHC subgroups

		F0 → F1				F1 → F2				F2 → F3				F3 → F4				scFPR				TTC*
	N	Mean	95% CI		I^2	Mean	95% CI		I^2	Mean	95% CI		I^2	Mean	95% CI		I^2	Mean	95% CI		I^2	(yrs)
All groups	131	0.107	0.097	0.118	98%	0.082	0.074	0.091	97%	0.117	0.107	0.129	94%	0.116	0.104	0.131	89%	0.094	0.088	0.100	85%	39
Study setting																						
Clinical	110	0.114	0.103	0.126	98%	0.086	0.077	0.096	98%	0.118	0.106	0.132	93%	0.119	0.105	0.133	89%	0.097	0.091	0.103	82%	37
Non-clinical	21	0.077	0.058	0.104	98%	0.065	0.053	0.081	96%	0.111	0.088	0.139	91%	0.101	0.068	0.150	94%	0.076	0.036	0.150	90%	47
Study design																						
Cross-sectional/Retrospective	88	0.114	0.101	0.129	98%	0.082	0.072	0.094	98%	0.119	0.107	0.133	93%	0.120	0.105	0.136	87%	0.097	0.090	0.104	84%	38
Retrospective-Prospective	43	0.093	0.079	0.110	98%	0.082	0.071	0.094	96%	0.114	0.094	0.138	95%	0.110	0.087	0.140	92%	0.088	0.078	0.098	85%	41
Study population**																						
Females	5	0.048	0.026	0.088	97%	0.051	0.043	0.061	27%*	0.071	0.049	0.103	47%*	0.051	0.025	0.106	46%*	0.053	0.036	0.078	53%*	74
Blood donors	3	0.067	0.017	0.264	96%	0.051	0.020	0.128	82%	0.094	0.018	0.487	83%	0.057	0.009	0.340	55%*	0.065	0.028	0.152	42%*	63
Pediatric patients	2	0.201	0.074	0.550	0%*	0.087	0.015	0.506	56%*	0.096	0.107	0.125	87%	0.055	0.028	0.585	0%*	0.133	0.009	1.984	0%*	45
Post transfusion	2	0.065	0.034	0.125	0%*	0.079	0.002	2.593	80%	0.114	0.038	0.341	0%*	0.134	0.033	0.545	0%*	0.081	0.028	0.230	0%*	44
Liver clinic	91	0.106	0.095	0.118	98%	0.082	0.072	0.092	98%	0.111	0.100	0.123	94%	0.112	0.100	0.127	88%	0.092	0.087	0.099	65%*	40
Injection drug users	10	0.109	0.071	0.168	99%	0.071	0.052	0.096	96%	0.121	0.086	0.170	92%	0.194	0.135	0.278	84%	0.094	0.072	0.123	88%	37
Community	4	0.134	0.082	0.218	94%	0.088	0.047	0.164	96%	0.111	0.074	0.167	83%	0.133	0.065	0.271	88%	0.104	0.086	0.125	22%*	35
Dialysis patients	6	0.121	0.060	0.244	95%	0.074	0.047	0.116	69%*	0.250	0.114	0.547	71%*	0.114	0.069	0.189	0%*	0.100	0.068	0.148	20%*	35
Renal transplant	4	0.225	0.094	0.540	89%	0.173	0.070	0.426	84%	0.190	0.074	0.490	64%*	0.117	0.041	0.331	0%*	0.190	0.076	0.475	60%*	24
Infectious diseases	4	0.144	0.084	0.247	89%	0.211	0.145	0.307	48%*	0.273	0.096	0.774	89%	0.256	0.047	1.379	92%	0.171	0.097	0.302	68%*	19
Publication year																						
<2000	4	0.068	0.030	0.154	96%	0.049	0.024	0.103	84%	0.124	0.058	0.264	48%*	0.172	0.058	0.513	48%*	0.068	0.033	0.143	61%*	49
2000 to <2005	56	0.119	0.101	0.140	98%	0.076	0.064	0.091	98%	0.116	0.101	0.132	91%	0.122	0.106	0.140	79%	0.095	0.087	0.105	83%	38
2005 to <2010	37	0.096	0.081	0.113	98%	0.085	0.074	0.097	94%	0.100	0.085	0.117	92%	0.092	0.074	0.114	89%	0.087	0.078	0.097	82%	43
≥2010	34	0.106	0.088	0.129	98%	0.096	0.080	0.116	97%	0.143	0.113	0.181	96%	0.137	0.102	0.184	95%	0.102	0.090	0.116	86%	34
Age at assessment																						
Age<40	23	0.128	0.096	0.172	98%	0.088	0.069	0.112	96%	0.142	0.114	0.177	86%	0.141	0.105	0.189	80%	0.113	0.095	0.134	78%	33
Age≥40	108	0.103	0.093	0.114	98%	0.081	0.072	0.091	98%	0.113	0.102	0.125	94%	0.113	0.099	0.127	90%	0.091	0.085	0.097	84%	40
Estimated age at infection																						
<20 years	11	0.097	0.060	0.155	98%	0.061	0.044	0.085	94%	0.118	0.082	0.170	84%	0.108	0.065	0.179	77%	0.083	0.063	0.110	75%*	45
20 to <30 years	95	0.100	0.090	0.112	98%	0.075	0.068	0.084	98%	0.104	0.095	0.115	93%	0.109	0.096	0.124	90%	0.088	0.083	0.094	83%	42
30 to <40 years	19	0.128	0.100	0.164	97%	0.127	0.099	0.163	95%	0.177	0.136	0.229	91%	0.146	0.115	0.185	75%*	0.124	0.104	0.146	79%	28
≥40 years	6	0.200	0.143	0.278	82%	0.147	0.090	0.239	83%	0.234	0.094	0.584	91%	0.246	0.098	0.619	78%	0.160	0.108	0.237	52%*	20
Estimated duration of infection																						
<10 years	8	0.218	0.162	0.295	90%	0.175	0.118	0.261	87%	0.290	0.136	0.619	89%	0.314	0.157	0.629	62%*	0.209	0.168	0.258	0%*	17
10 to <20 years	71	0.128	0.113	0.145	98%	0.081	0.070	0.094	98%	0.130	0.116	0.145	89%	0.133	0.117	0.152	82%	0.106	0.099	0.114	75%*	35
≥20 years	52	0.075	0.067	0.084	97%	0.075	0.067	0.084	95%	0.092	0.080	0.104	89%	0.090	0.076	0.106	91%	0.076	0.071	0.081	70%*	49
HCV genotype																						
Genotype-1	10	0.072	0.049	0.108	98%	0.074	0.052	0.107	96%	0.072	0.061	0.083	58%*	0.056	0.029	0.107	92%	0.072	0.055	0.093	83%	59
Genotype non-1	6	0.096	0.065	0.142	93%	0.091	0.070	0.117	76%	0.102	0.069	0.149	79%	0.175	0.112	0.274	63%*	0.096	0.072	0.128	65%*	37
Genotype-3	3	0.134	0.084	0.213	77%	0.103	0.084	0.126	2%*	0.112	0.049	0.253	83%	0.247	0.165	0.370	0%*	0.119	0.080	0.175	36%*	30
Genotype non-3	15	0.079	0.060	0.103	98%	0.079	0.062	0.102	95%	0.076	0.067	0.087	66%*	0.073	0.043	0.122	93%	0.077	0.065	0.092	78%	52

Table 2. Annual fibrosis progression rates based on random-effects meta-analyses. The meta-analysis was restricted to 131 study groups where CHC was confirmed by HCV RNA testing in all subjects. *Abbreviations: scFPR: stage-constant annual progression rate (assuming linear progression from stage F0 to F4); I^2: the proportion of variability in progression rates due to heterogeneity vs. sampling error; N: number of groups included in the meta-analysis; *TTC: time-to-cirrhosis (based on unadjusted stage-specific FPRs).* *Study subgroups with low-to-moderate heterogeneity; **Study populations are ordered by progression from slow to fast based on TTC. Notes: The estimates are not adjusted for covariates and maybe confounded; genotype non-1 and non-3 groups are composed of 65% genotype-3 and 82% genotype-1 respectively; the size of CIs of each subgroup depend on the N. of studies, study size, and the extent of heterogeneity across the studies included in the subgroup.

Table 3: Random-effects meta-regression of covariates associated with hepatic fibrosis progression rates

Covariates	F0→F1*				F1→F2*				F2→F3*				F3→F4*				scFPR*			
	β	SE	P-value	RR	β	SE	P-value	RR	β	SE	P-value	RR	β	SE	P-value	RR	β	SE	P-value	RR
Intercept	-2.564	0.555	<.0001		-3.482	0.675	<.0001		-1.031	0.608	0.093		-1.400	0.766	0.071		-2.438	0.312	<.0001	
Study design																				
Cross-sectional/Retro (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
Retrospective-Prospective	-0.088	0.093	0.347	*0.92*	0.041	0.113	0.717	*1.04*	-0.001	0.100	0.991	*1.00*	0.036	0.126	0.773	*1.04*	0.011	0.050	0.834	*1.01*
Study population																				
Liver clinic (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
Females	-0.149	0.334	0.656	*0.86*	0.318	0.400	0.428	*1.37*	-0.073	0.349	0.834	*0.93*	-0.616	0.442	0.166	*0.54*	-0.046	0.170	0.790	*0.96*
Blood donors	-0.040	0.256	0.875	*0.96*	-0.318	0.314	0.313	*0.73*	-0.276	0.289	0.342	*0.76*	-0.707	0.395	0.076	*0.49*	-0.175	0.166	0.296	*0.84*
Pediatric patients	0.361	0.475	0.449	*1.43*	0.831	0.567	0.145	*2.30*	-0.054	0.521	0.918	*0.95*	-0.199	0.750	0.791	*0.82*	0.479	0.307	0.121	*1.61*
Post-transfusion	-0.343	0.407	0.402	*0.71*	-0.206	0.493	0.676	*0.81*	-0.143	0.466	0.760	*0.87*	-0.853	0.651	0.192	*0.43*	-0.093	0.282	0.742	*0.91*
Injecting drug users	0.278	0.221	0.211	*1.32*	-0.310	0.268	0.251	*0.73*	0.120	0.243	0.621	*1.13*	0.499	0.293	0.091	*1.65*	0.070	0.115	0.543	*1.07*
Community	0.226	0.209	0.283	*1.25*	0.167	0.248	0.503	*1.18*	0.016	0.204	0.938	*1.02*	0.192	0.241	0.428	*1.21*	0.125	0.087	0.154	*1.13*
Dialysis patients	-0.121	0.203	0.551	*0.89*	-0.550	0.248	**0.028**	***0.58***	0.299	0.250	0.233	*1.35*	-0.103	0.307	0.738	*0.90*	-0.235	0.153	0.127	*0.79*
Renal transplant recipients	-0.012	0.236	0.961	*0.99*	0.262	0.285	0.359	*1.30*	0.064	0.274	0.815	*1.07*	-0.372	0.412	0.368	*0.69*	0.164	0.191	0.390	*1.18*
Infectious diseases	-0.261	0.241	0.282	*0.77*	0.304	0.294	0.304	*1.35*	0.264	0.257	0.305	*1.30*	0.211	0.314	0.502	*1.24*	-0.013	0.139	0.924	*0.99*
Publication year																				
<2000 (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
2000 to <2005	0.406	0.241	0.094	*1.50*	0.116	0.299	0.698	*1.12*	-0.010	0.295	0.973	*0.99*	-0.543	0.369	0.143	*0.58*	0.227	0.164	0.169	*1.25*
2005 to <2010	0.492	0.242	**0.044**	***1.64***	0.352	0.300	0.242	*1.42*	-0.009	0.297	0.975	*0.99*	-0.583	0.372	0.120	*0.56*	0.310	0.165	0.062	*1.36*
≥2010	0.404	0.246	0.103	*1.50*	0.356	0.306	0.246	*1.43*	0.227	0.301	0.451	*1.26*	-0.500	0.377	0.187	*0.61*	0.369	0.166	**0.028**	***1.45***
Gender – male†	0.592	0.437	0.178	*1.81*	0.704	0.520	0.179	*2.02*	-0.103	0.454	0.822	*0.90*	-0.157	0.564	0.781	*0.85*	0.289	0.217	0.186	*1.34*
Age at HCV infection (yrs.)	0.004	0.011	0.698	*1.00*	0.033	0.013	**0.012**	***1.03***	0.012	0.011	0.292	*1.01*	0.020	0.014	0.169	*1.02*	0.014	0.006	**0.014**	***1.01***
Duration of infection (yrs.)	-0.063	0.010	**<.0001**	***0.94***	-0.028	0.012	**0.022**	***0.97***	-0.048	0.010	**<.0001**	***0.95***	-0.043	0.013	**0.001**	***0.96***	-0.049	0.005	**<.0001**	***0.95***
Injecting drug use†	0.194	0.248	0.435	*1.21*	-0.114	0.298	0.701	*0.89*	-0.117	0.262	0.656	*0.89*	0.301	0.328	0.361	*1.35*	0.090	0.132	0.497	*1.09*
Blood transfusion†	0.862	0.298	**0.005**	***2.37***	0.260	0.355	0.466	*1.30*	0.219	0.302	0.469	*1.25*	0.464	0.369	0.211	*1.59*	0.486	0.145	**0.001**	***1.63***
Excess alcohol use†	-0.312	0.263	0.238	*0.73*	0.591	0.314	0.062	*1.81*	0.177	0.273	0.517	*1.19*	0.245	0.329	0.458	*1.28*	0.201	0.131	0.126	*1.22*
HIV positive†	0.075	0.839	0.929	*1.08*	0.532	1.009	0.599	*1.70*	-0.506	0.907	0.578	*0.60*	0.191	1.105	0.863	*1.21*	-0.312	0.429	0.469	*0.73*
Genotype-1†	0.473	0.221	**0.034**	***1.61***	-0.380	0.264	0.153	*0.68*	-0.539	0.224	**0.018**	***0.58***	-0.313	0.274	0.256	*0.73*	-0.051	0.108	0.637	*0.95*
Genotype-3†	0.226	0.277	0.416	*1.25*	0.036	0.331	0.914	*1.04*	-0.273	0.285	0.341	*0.76*	0.194	0.347	0.577	*1.21*	0.093	0.133	0.487	*1.10*
White†	0.160	0.197	0.420	*1.17*	-0.047	0.238	0.845	*0.95*	-0.325	0.208	0.120	*0.72*	0.032	0.256	0.900	*1.03*	-0.045	0.102	0.660	*0.96*
Black†	-0.302	0.273	0.272	*0.74*	0.332	0.330	0.317	*1.39*	-0.011	0.287	0.970	*0.99*	-0.609	0.356	0.089	*0.54*	-0.005	0.139	0.971	*0.99*
Asian†	0.086	0.354	0.808	*1.09*	0.268	0.431	0.534	*1.31*	0.003	0.404	0.994	*1.00*	0.933	0.534	0.083	*2.54*	0.061	0.242	0.800	*1.06*
I^2_{Res}		*96%*				*96%*				*86%*				*77%*				*39%*		
Adjusted R^2		*56%*				*38%*				*54%*				*53%*				*87%*		

Table 3. Linear mixed model-maximum likelihood method. *Log progression rates. †Proportion. Values in bold indicate statistical significance. *Abbreviations: scFPR: stage-constant annual fibrosis progression rates (assuming linear progression from F0 to F4); β: coefficient; SE: standard error; HIV: human immunodeficiency virus; RNA: ribonucleic acid; ref: reference category; adjusted R^2: the proportion of heterogeneity explained by covariates in the model; I^2_{res}: the proportion of residual variability due to heterogeneity.*

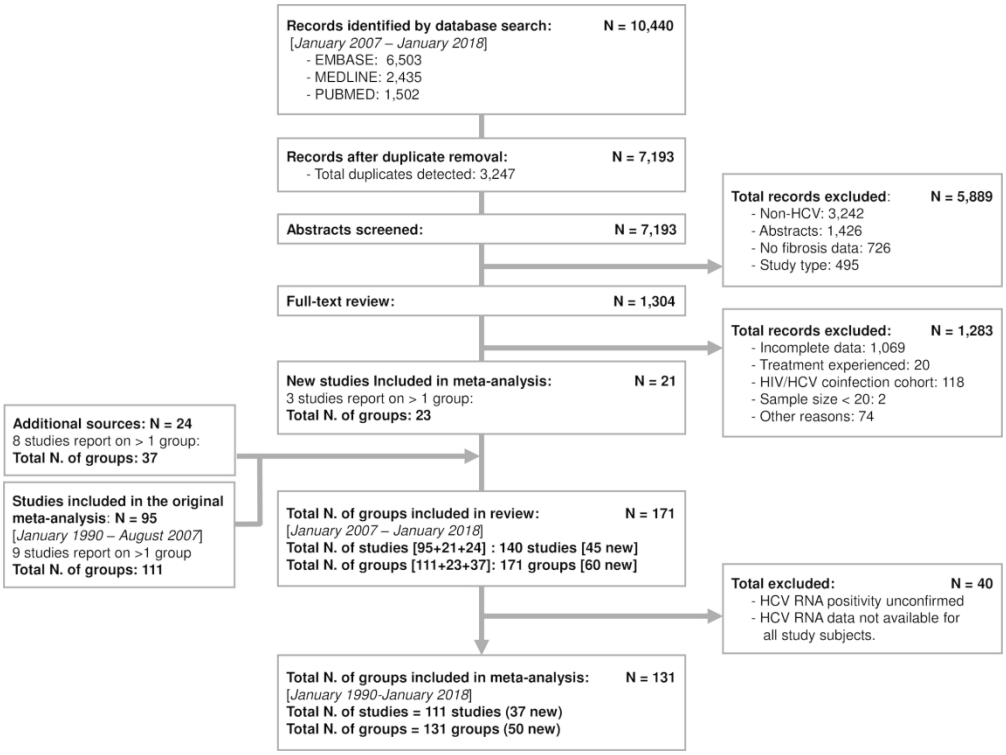
Figure legends

Fig 1. PRISMA flow diagram showing the study selection progress.

The literature search recovered a total of 5,718 citations. Following duplicate removal and supplementary citation searches, the review process identified a total of 45 new studies reporting on 60 groups of HCV-infected patients. Together with the 95 studies reporting on 111 groups identified by the original review, the current update identified a total of 140 studies of 171 HCV-infected groups of patients. Meta-analysis was restricted to 111 studies reporting on 131 study groups where CHC was confirmed by HCV RNA testing in all subjects.

Fig 2. Cumulative probability of cirrhosis for various patient populations.

Figure showing the cumulative probability of cirrhosis over years of HCV infection for (A) all study groups by estimation method; and groups stratified by (B) study setting; (C) viral genotype; and (D) study population using stage-specific progression rate estimates. Cumulative probabilities are projected using unadjusted estimates and may be confounded. Note: a high degree of heterogeneity is present within the liver clinic, injection drug use and community populations, as well for genotype-1 infected groups and for studies stratified by study setting.



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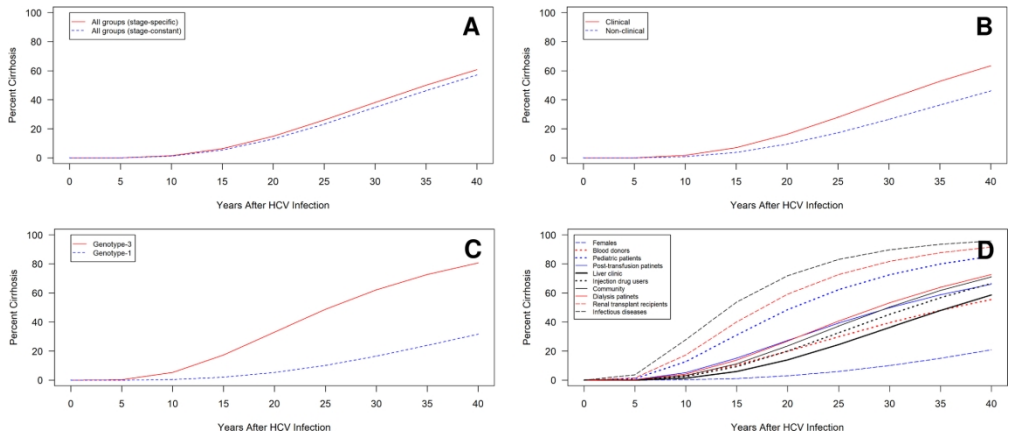

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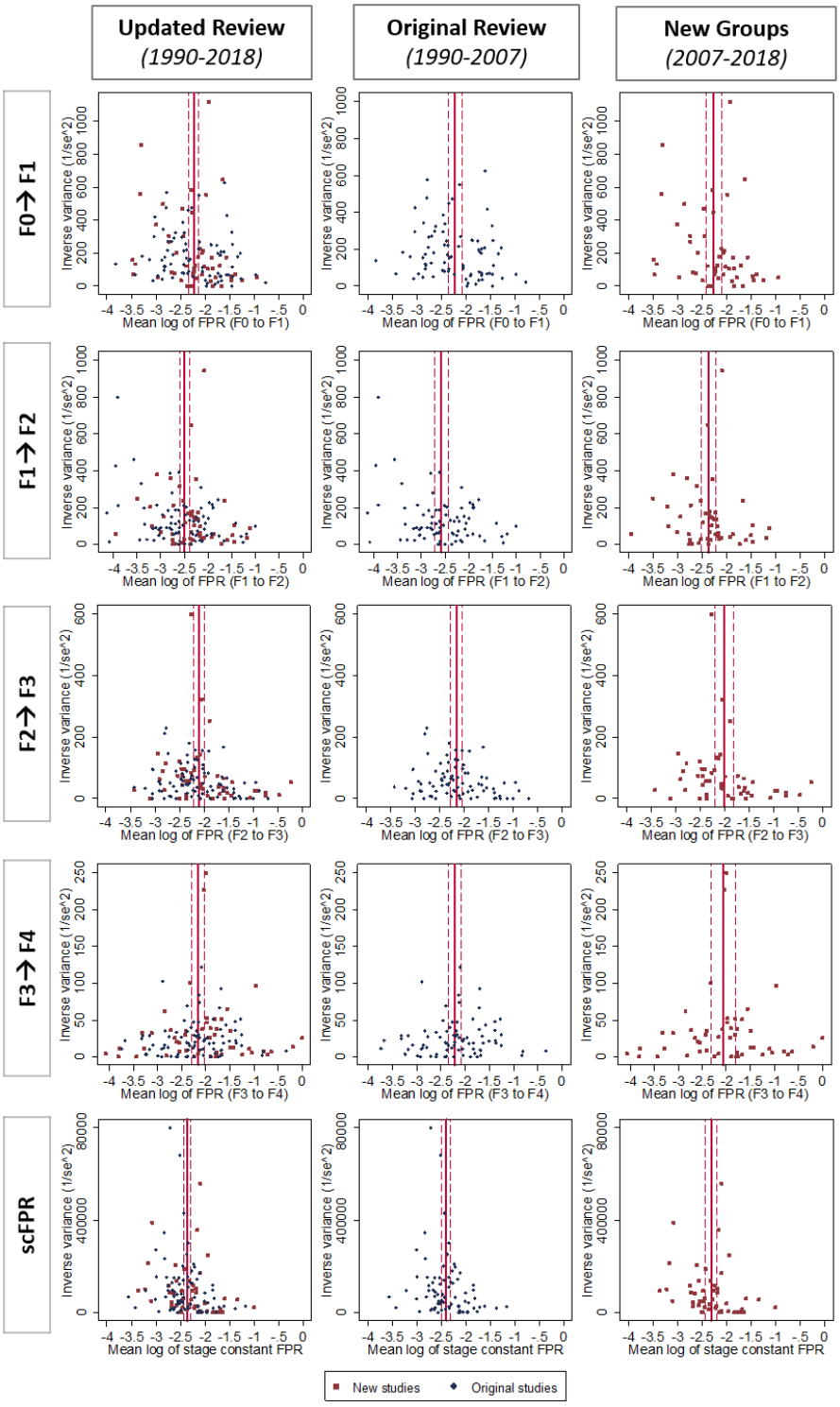
190x80mm (300 x 300 DPI)

Supplementary Materials

List of Supplementary Materials:

Supplementary Materials

S1 Figure: Funnel plots for hepatic fibrosis progression rate



Supplementary Figure 1. Funnel plots of stage-specific and stage-constant (sc) FPRs for the 131 study groups included in the meta-analysis stratified by study update. Funnel plots were generated by plotting the natural log of FPRs against inverse variance.

Supplementary Materials

S1 Table: General definitions of study type, setting, and population

Study design	
Cross-sectional/retrospective:	Patients with liver disease presenting for clinical care, usually at tertiary care centers, where efforts were made to track the liver disease responsible for the referral back to the presumed time of infection, based on the history of receipt of blood or blood product or of the first use of injection drugs [1–17].
Retrospective-prospective:	Studies that identify groups of individuals who, in the past, were either asymptomatic or had developed recognized acute hepatitis C following an outbreak of HCV infection from a recognized source, who could be traced retrospectively, recontacted, and then followed-up prospectively [18–41].
Study setting	
Clinical:	Individuals who were identified and/or assessed for their HCV status and liver disease in a clinical/tertiary care setting [2,3,12,14–16,20,21,23–26,4,27,30,35,36,38,39,41–44,5–11].
Nonclinical:	Individuals who were screened for HCV in a nonclinical setting, for example, blood donation center or regional center [1,13,17–19,22,28,29,37,40].
Study population:	
Community:	HCV-infected individuals identified or participating in national health screening or studies conducted in nonclinical settings [18,45].
Liver clinic:	HCV-infected individuals referred to specialist liver clinics for further assessment [1,4,23–27,30,33,35,39,41,9,42,44,11,12,14–16,20,21].
Blood donors:	Individuals newly diagnosed with chronic HCV infection at blood donor screening [19,37].
Dialysis patients:	HCV-infected individuals with end-stage renal disease receiving dialysis and awaiting renal transplantation [2,31,34].
Injecting drug users:	Individuals who acknowledged injection drug use as the main risk factor for HCV infection – not only active users [17,28,29,40,43].
Female cohorts:	Population of otherwise healthy females infected with HCV [13].
Pediatric population:	Population of children infected with HCV [10,36].
Post-transfusion cohorts:	Population infected with HCV post-transfusion [8,22].
Renal transplant:	Population renal transplant recipients infected with HCV [32,38].
Infectious diseases:	HCV infected individuals managed at Infectious diseases unit [3,5–7].
General:	
Presumed date of HCV infection	Date of transfusion of blood or blood products prior to 1992, when serologic screening for HCV became widely available, the first year of injecting drug use, or the date of a single and convincing parenteral exposure (e.g. needle-stick injury).
Estimated duration of HCV infection	Time elapsed from the presumed date of infection to the date of liver biopsy. Estimated only for individuals with known risk factors.
Elevated ALT levels	ALT values abnormally elevated (more than the upper limit of normal values) at entry and at least once during the 6 months prior to screening.
Excess alcohol consumption	Accepted the definitions reported in the studies. Alcohol consumption of at least more than 20 g/day in the past 12 months of study entry.

Supplementary Table 1. Abbreviations: HCV: hepatitis C virus; ALT: alanine aminotransferase. References provided for newly identified studies only.

Supplementary Materials

S2 Table: Fibrosis scoring systems for HCV

HCV disease severity	Liver Biopsy (LB)				Transient Elastography (TE)		
	Histological Scoring Systems				Liver Stiffness Measurement (LSM)		
	METAVIR		Knodell	Ishak	LSM cut-off (kPa)	AUROC	References
No fibrosis	**No fibrosis**	**F0**	F0	0	<7.1	-	[46]
Mild fibrosis	**Portal fibrosis without septa**	**F1**	F1	1	<7.1	-	
Moderate fibrosis	**Portal fibrosis with rare septa**	**F2**	F3	2	7.1-9.5	0.83	
Severe fibrosis	**Numerous septa without cirrhosis**	**F3**	F3	3-4	9.5-12.5	0.84	
Cirrhosis	**Cirrhosis**	**F4**	F4	5-6	≥12.5	0.95	

Supplementary Table 2**.** Table showing the criteria used to convert various invasive and non-invasive scoring systems to the well-validated METAVIR system. Majority of study groups (124 out of 131 study groups included in the meta-analysis) assessed hepatic fibrosis using histology; only 7 performed a non-invasive assessment of hepatic fibrosis (6 used LSM and 1 used a combination of LSM, LB and APRI). Studies that reported composite scores i.e., F0/F1 were distributed 50:50 across F0 and F1. *Abbreviations: LB: liver biopsy; TE: transient elastography/FibroScan; LSM: liver stiffness measurement; LB: liver biopsy; APRI: AST to platelet ratio index; METAVIR: meta-analysis of histological data in viral hepatitis; AUROC: area under the receiver operator curve.*

Supplementary Materials

List of 45 studies identified by the updated review ordered by study ID:

1. Agostini, H., Castera, L., Melin, P., Cattan, L. & Roudot-Thoraval, F. HEPACOM: multicenter, observational prospective study of outcome and monitoring of HCV positive antiviral-naive patients managed in the French health care system. *Gastroenterologie clinique et biologique* **31,** 1074–1080 (2007).

2. Allison, R. D. *et al.* A 25-year study of the clinical and histologic outcomes of hepatitis C virus infection and its modes of transmission in a cohort of initially asymptomatic blood donors. **206,** 654–661 (2012).

3. Boonwaat, L., Haber, P. S., Levy, M. H. & Lloyd, A. R. Establishment of a successful assessment and treatment service for Australian prison inmates with chronic hepatitis C. *Med J Aust* **192,** 496–500 (2010).

4. Bourliere, M. *et al.* Pegylated interferon-alpha2a plus ribavirin for chronic hepatitis C in a real-life setting: the Hepatys French cohort (2003-2007). *Antivir Ther* **17,** 101–110 (2012).

5. Contreras, A. M. *et al.* End-stage renal disease and hepatitis C infection: comparison of alanine aminotransferase levels and liver histology in patients with and without renal damage. *Annals of hepatology* **6,** 48–54 (2007).

6. Delgado-Borrego, A. *et al.* Influence of body mass index on outcome of pediatric chronic hepatitis C virus infection. *J Pediatr Gastroenterol Nutr* **51,** 191–197 (2010).

7. Forestier, N. *et al.* Acoustic radiation force impulse imaging for evaluation of antiviral treatment response in chronic hepatitis C. *J. Gastrointest. Liver Dis.* **21,** 367–373 (2012).

8. Goodman, Z. D. *et al.* Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial. *Hepatology* **47,** 836–843 (2008).

9. Hui, C.-K. *et al.* Disease progression in Chinese chronic hepatitis C patients with persistently normal alanine aminotransaminase levels. *Alimentary pharmacology & therapeutics* **25,** 1283–1292 (2007).

10. Liu, T. *et al.* Marijuana use in hepatitis C infection does not affect liver biopsy histology or treatment outcomes. **28,** 381–384 (2014).

11. Nanda, K. S. *et al.* Elevated circulating osteoprotegerin and reduced matrix-metalloprotease-9 in post-menopausal women with chronic Hepatitis C virus infection. *Cytokine* **60,** 328–333 (2012).

12. Rao, H.-Y. *et al.* Outcome of hepatitis C virus infection in Chinese paid plasma donors: a 12-19-year cohort study. *Journal of gastroenterology and hepatology* **27,** 526–532 (2012).

13. Siddiqui, F. A. *et al.* Demographics of a large cohort of urban chronic hepatitis C patients. *Hepatology international* **2,** 376–381 (2008).

14. Werner, T. *et al.* Treatment of hepatitis C in renal transplantation candidates: a single-center experience. *Transplantation* **90,** 407–411 (2010).

15. Bochud, P.-Y. *et al.* Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. *J. Hepatol.* **51,** 655–66 (2009).

16. Hissar, S. S. *et al.* Natural history of hepatic fibrosis progression in chronic hepatitis C virus infection in India. *J Gastroenterol Hepatol* **24,** 581–587 (2009).

17. Kallwitz, E. R. *et al.* Ethnicity and body mass index are associated with hepatitis C presentation and progression. *Clin Gastroenterol Hepatol* **8,** 72–78 (2010).

18. Kielland, K. B. *et al.* Liver fibrosis progression at autopsy in injecting drug users infected by hepatitis C: a longitudinal long-term cohort study. *J Hepatol* **60,** 260–266 (2014).

19. Larsen, C. *et al.* Hepatitis C virus genotype 3 and the risk of severe liver disease in a large population of drug users in France. *J Med Virol* **82,** 1647–1654 (2010).

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20. Lawson, A. & Trent Hepatitis, C. S. G. Hepatitis C virus-infected patients with a persistently normal alanine aminotransferase: do they exist and is this really a group with mild disease? *J Viral Hepat* **17,** 51–58 (2010).

21. Marabita, F. *et al.* Genetic variation in the interleukin-28B gene is not associated with fibrosis progression in patients with chronic hepatitis C and known date of infection. *Hepatology* **54,** 1127–1134 (2011).

22. Patin, E. *et al.* Genome-wide association study identifies variants associated with progression of liver fibrosis from HCV infection. *Gastroenterology* **143,** 1212–1244 (2012).

23. Brescini, L. *et al.* Evaluating Liver Fibrosis by Transient Elastometry in Patients With HIV-HCV Coinfection and Monoinfection. *Hepat. Mon.* **14,** e15426 (2014).

24. de Lédinghen, V. *et al.* Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy. *J. Viral Hepat.* **15,** 427–33 (2008).

25. Nunnari, G. Circulating fibrocytes as a marker of liver fibrosis in chronic hepatitis C. *Front. Biosci.* **E2,** 1241 (2010).

26. Mazzocato, S. *et al.* Comparison of liver fi brosis progression in HIV / HCV co-infected and HCV mono-infected patients by transient elastometry. **39,** 797–802 (2014).

27. Suárez-Zarracina, T. *et al.* Didanosine (ddI) associates with increased liver fibrosis in adult HIV-HCV coinfected patients. *J. Viral Hepat.* **19,** 685–93 (2012).

28. White, D. L. *et al.* Higher serum testosterone is associated with increased risk of advanced hepatitis C-related liver disease in males. *Hepatology* **55,** 759–68 (2012).

29. Reggiardo, M. V. *et al.* Natural history of hepatitis C virus infection in a cohort of asymptomatic post-transfused subjects. *Ann. Hepatol.* **11,** 658–66 (2015).

30. Liu, S., Cheng, M., Mu, M. & Yang, Q. [Natural clearance of hepatitis C virus in 96 patients with infection acquired by blood transfusion from a single donor in Guizhou]. *Zhonghua Gan Zang Bing Za Zhi* **22,** 251–4 (2014).

31. Terrault, N. A. *et al.* Fibrosis progression in African Americans and Caucasian Americans with chronic hepatitis C. *Clin Gastroenterol Hepatol* **6,** 1403–1411 (2008).

32. Guyader, D. *et al.* Liver iron is a surrogate marker of severe fibrosis in chronic hepatitis C. *J. Hepatol.* **46,** 587–95 (2007).

33. Pradat, P., Voirin, N., Tillmann, H. L., Chevallier, M. & Trépo, C. Progression to cirrhosis in hepatitis C patients: An age-dependent process. *Liver Int.* **27,** 335–339 (2007).

34. Castéra, L. *et al.* Effect of antiviral treatment on evolution of liver steatosis in patients with chronic hepatitis C: indirect evidence of a role of hepatitis C virus genotype 3 in steatosis. *Gut* **53,** 420–4 (2004).

35. Mathurin, P. Slow progression rate of fibrosis in hepatitis C virus patients with persistently normal alanine transaminase activity. *Hepatology* **27,** 868–872 (1998)

36. Bruden DJ, McMahon BJ, Townshend-Bulson L, et al. Risk of End Stage Liver Disease, Hepatocellular Carcinoma and Liver-Related Death By Fibrosis Stage in the Hepatitis C Alaska Cohort. Hepatology. 2017. doi:10.1002/hep.29115.

37. Cepeda JA, Thomas DL, Astemborski J, Kong X, Kirk GD, Mehta SH. Liver disease progression in a community-based sample of HCV-infected PWID. Top Antivir Med. 2016;24 (E-1):218.

38. Cepeda JA, Thomas DL, Astemborski J, Sulkowski MS, Kirk GD, Mehta SH. Increased mortality among persons with chronic hepatitis C with moderate or severe liver disease: a cohort study. Clin Infect Dis. 2017;10:10. doi:https://dx.doi.org/10.1093/cid/cix207.

39. Sakellariou S, Boletis JN, Sypsa V, Psichogiou M, Tiniakos D, Delladetsima I. Histological features of chronic hepatitis C in haemodialysis patients. Liver Int. 2014;34(6):e56-61. doi:https://dx.doi.org/10.1111/liv.12413.

40. Lemos LB, Perez RM, Lemos MM, et al. Hepatitis C in chronic kidney disease: predialysis patients present

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NOTE: Studies that reported results in subgroups, which may influence disease progression were extracted separately. Also, Of the 45 identiied studies, only studies that established HCV RNA positivity for all study subjects were included in the meta-anlaysis.

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S3 Table: Table summarizing study characteristics of the 45 identified studies

Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
1	**Agostini 2007** [18]	2007	France	English	Community	Non-clinical	R-P	3794	1283	LB	METAVIR	$FPR_{0\to1}$:0.119 $FPR_{1\to2}$:0.182 $FPR_{2\to3}$:0.186 $FPR_{3\to4}$:0.069 ScFPR: 0.137
2	**Allison 2012** [19]	2012	USA	English	Blood donor	Non-clinical	R-P	185	185	LB	Ishak	$FPR_{0\to1}$:0.044 $FPR_{1\to2}$:0.072 $FPR_{2\to3}$:0.047 $FPR_{3\to4}$:0.022 ScFPR: 0.050
3	**Boonwaat 2010** [1]	2010	Australia	English	Liver clinic/prison	Non-clinical	C-S/R	371	153	LB	METAVIR	$FPR_{0\to1}$:0.085 $FPR_{1\to2}$:0.114 $FPR_{2\to3}$:0.148 $FPR_{3\to4}$:0.047 ScFPR: 0.095
4	**Bourliere 2012** [30]	2012	France	English	Liver clinic	Clinical	R-P	2066	1794	LB	METAVIR	$FPR_{0\to1}$:0.118 $FPR_{1\to2}$:0.101 $FPR_{2\to3}$:0.084 $FPR_{3\to4}$:0.111 ScFPR: 0.100
5	**Contreras 2007** [2]	2007	Mexico	English	Dialysis patients	Clinical	C-S/R	64	64	LB	Ishak	$FPR_{0\to1}$:0.113 $FPR_{1\to2}$:0.205 $FPR_{2\to3}$:0.103 $FPR_{3\to4}$:0.123 ScFPR: 0.130
6	**Delgado-Borego 2010** [47]	2010	USA	English	Pediatric	Clinical	C-S/R	102	102	LB	METAVIR	$FPR_{0\to1}$:0.203 $FPR_{1\to2}$:0.071 $FPR_{2\to3}$:0.220 $FPR_{3\to4}$:0.034 ScFPR: 0.131
7	**Forestier 2012** [35]	2012	France	English	Liver clinic	Clinical	R-P	98	45	LB	METAVIR	$FPR_{0\to1}$:0.208 $FPR_{1\to2}$:0.122 $FPR_{2\to3}$:0.123 $FPR_{3\to4}$:0.219 ScFPR: 0.152
8	**Goodman 2008** [36]	2008	USA	English	Pediatric	Clinical	R-P	121	121	LB	Knodell	$FPR_{0\to1}$:0.200 $FPR_{1\to2}$:0.106 $FPR_{2\to3}$:0.038 $FPR_{3\to4}$:0.129 ScFPR: 0.137
9	**Hui 2007** [11]	2007	China	English	Liver clinic	Clinical	C-S/R	82	53	LB	METAVIR	$FPR_{0\to1}$:0.033 $FPR_{1\to2}$:0.042 $FPR_{2\to3}$:0.095 $FPR_{3\to4}$:0.072 ScFPR: 0.041

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Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
10a	**Liu 2014 – M** [12]	2014	Canada	English	Liver clinic	Clinical	C-S/R	102	102	LB	Batts and Ludwig	FPR $_{0\to1}$:0.145 FPR $_{1\to2}$:0.159 FPR $_{2\to3}$:0.083 FPR $_{3\to4}$:0.123 ScFPR: 0.130
10b	**Liu 2014 – M** [12]	2014	Canada	English	Liver clinic	Clinical	C-S/R	275	275	LB	Batts and Ludwig	FPR $_{0\to1}$:0.145 FPR $_{1\to2}$:0.109 FPR $_{2\to3}$:0.071 FPR $_{3\to4}$:0.102 ScFPR: 0.110
11	**Nanda 2012** [13]	2012	Ireland	English	Female	Non-clinical	C-S/R	20	20	LB	Ishak	FPR $_{0\to1}$:0.023 FPR $_{1\to2}$:0.046 FPR $_{2\to3}$:0.098 FPR $_{3\to4}$:0.164 ScFPR: 0.033
12	**Rao 2012** [37]	2012	China	English	Blood donor	Non-clinical	R-P	348	175	LSM	METAVIR	FPR $_{0\to1}$:0.054 FPR $_{1\to2}$:0.082 FPR $_{2\to3}$:0.116 FPR $_{3\to4}$:0.113 ScFPR: 0.068
13a	**Siddiqui 2008** [14]	2008	USA	English	Liver clinic	Clinical	C-S/R	2035	1009	LB	METAVIR	FPR $_{0\to1}$:0.077 FPR $_{1\to2}$:0.088 FPR $_{2\to3}$:0.143 FPR $_{3\to4}$:0.138 ScFPR: 0.087
13b	**Siddiqui 2008** [14]	2008	USA	English	Liver clinic	Clinical	C-S/R	616	356	LB	METAVIR	FPR $_{0\to1:}$ 0.076 FPR $_{1\to2}$:0.102 FPR $_{2\to3}$:0.153 FPR $_{3\to4}$:0.190 ScFPR: 0.93
14	**Werner 2010** [38]	2010	USA	English	Renal transplant	Clinical	R-P	22	22	LB	Batts and Ludwig	FPR $_{0\to1}$:0.293 FPR $_{1\to2}$:0.230 FPR $_{2\to3}$:0.356 FPR $_{3\to4}$:0.336 ScFPR: 0.277
15a	**Bochud 2009** [39]	2009	Switzerland	English	Liver clinic	Clinical	^{14}R-P	607	607	LB	METAVIR	FPR $_{0\to1}$:0.094 FPR $_{1\to2}$:0.067 FPR $_{2\to3}$:0.073 FPR $_{3\to4}$:0.125 ScFPR: 0.080
15b	**Bochud 2009** [39]	2009	Switzerland	English	Liver clinic	Clinical	R-P	90	90	LB	METAVIR	FPR $_{0\to1}$:0.082 FPR $_{1\to2}$:0.84 FPR $_{2\to3}$:0.066 FPR $_{3\to4}$:0.082 ScFPR: 0.077

Supplementary Table 7 continued

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Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
15c	**Bochud 2009** [39]	2009	Switzerland	English	Liver clinic	Clinical	R-P	312	312	LB	METAVIR	$FPR_{0\to1}$:0.115 $FPR_{1\to2}$:0.096 $FPR_{2\to3}$:0.080 $FPR_{3\to4}$:0.199 ScFPR: 0.101
15d	**Bochud 2009** [39]	2009	Switzerland	English	Liver clinic	Clinical	R-P	117	117	LB	METAVIR	$FPR_{0\to1}$:0.081 $FPR_{1\to2}$:0.075 $FPR_{2\to3}$:0.080 $FPR_{3\to4}$:0.167 ScFPR: 0.079
16	**Hissar 2009** [15]	2009	India	English	Liver clinic	Clinical	C-S/R	213	213	LB	Knodell	$FPR_{0\to1}$:0.253 $FPR_{1\to2}$:0.166 $FPR_{2\to3}$:0.220 $FPR_{3\to4}$:0.160 ScFPR: 0.192
17	**Kallwitz 2010** [16]	2010	USA	English	Liver clinic	Clinical	C-S/R	812	812	LB	METAVIR	$FPR_{0\to1}$:0.087 $FPR_{1\to2}$:0.162 $FPR_{2\to3}$:0.110 $FPR_{3\to4}$:0.111 ScFPR: 0.099
18	**Kielland 2014** [40]	2014	Norway	English	IDU	Non-clinical	R-P	61	61	LB	METAVIR	$FPR_{0\to1}$:0.122 $FPR_{1\to2}$:0.022 $FPR_{2\to3}$:0.448 $FPR_{3\to4}$:0.270 ScFPR: 0.077
19a	**Larsen 2010** [17]	2010	France	English	IDU	Non-clinical	C-S/R	1077	493	LB	METAVIR	$FPR_{0\to1}$:0.166 $FPR_{1\to2}$:0.104 $FPR_{2\to3}$:0.154 $FPR_{3\to4}$:0.273 ScFPR: 0.133
19b	**Larsen 2010** [17]	2010	France	English	IDU	Non-clinical	C-S/R	1986	1108	LB	METAVIR	$FPR_{0\to1}$:0.138 $FPR_{1\to2}$:0.065 $FPR_{2\to3}$:0.106 $FPR_{3\to4}$:0.267 ScFPR: 0.101
20a	**Lawson 2010** [41]	2010	UK	English	Liver clinic	Clinical	R-P	87	39	LB	Ishak	$FPR_{0\to1}$:0.038 $FPR_{1\to2}$:0.066 $FPR_{2\to3}$:0.158 $FPR_{3\to4}$:0.380 ScFPR: 0.049
20b	**Lawson 2010** [41]	2010	UK	English	Liver clinic	Clinical	R-P	1140	459	LB	Ishak	$FPR_{0\to1}$:0.071 $FPR_{1\to2}$:0.152 $FPR_{2\to3}$:0.342 $FPR_{3\to4}$:0.198 ScFPR: 0.108

Supplementary Table 7 continued

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Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
21	**Marabita 2011** [20]	2011	Italy	English	Liver clinic	Clinical	R-P	247	247	LB	Ishak	$FPR_{0\to1}$:0.193 $FPR_{1\to2}$:0.062 $FPR_{2\to3}$:0.067 $FPR_{3\to4}$:0.076 ScFPR : 0.088
22a	**Patin 2012-French cohort** [42]	2012	France	English	Liver clinic	Clinical	R-P	467	467	LB	METAVIR	$FPR_{0\to1}$:0.121 $FPR_{1\to2}$:0.042 $FPR_{2\to3}$:0.530 $FPR_{3\to4}$:0.081 ScFPR : 0.089
22b	**Patin 2012-Swiss cohort** [42]	2012	Switzerland	English	Liver clinic	Clinical	R-P	694	614	LB	METAVIR	$FPR_{0\to1}$:0.093 $FPR_{1\to2}$:0.067 $FPR_{2\to3}$:0.058 $FPR_{3\to4}$:0.905 ScFPR : 0.081
22c	**Patin 2012-US/France** [42]	2012	US/France	English	Liver clinic	Clinical	R-P	320	320	LB	METAVIR	$FPR_{0\to1}$:0.088 $FPR_{1\to2}$:0.063 $FPR_{2\to3}$:0.099 $FPR_{3\to4}$:0.063 ScFPR : 0.076
22d	**Patin 2012-International** [42]	2012	Australia/ Germany/ UK	English	Liver clinic	Clinical	R-P	642	642	LB	METAVIR	$FPR_{0\to1}$:0.103 $FPR_{1\to2}$:0.076 $FPR_{2\to3}$:0.087 $FPR_{3\to4}$:0.139 ScFPR : 0.091
22e	**Patin 2012-Australian** [42]	2012	Australia	English	Liver clinic	Clinical	R-P	219	219	LB	METAVIR	$FPR_{0\to1}$:0.140 $FPR_{1\to2}$:0.088 $FPR_{2\to3}$:0.077 $FPR_{3\to4}$:0.134 ScFPR : 0.102
23	**Brescini 2014**	2014	Italy	English	Infectious diseases	Clinical	C-S/R	186	186	LSM	METAVIR	$FPR_{0\to1}$:0.192 $FPR_{1\to2}$:0.246 $FPR_{2\to3}$:0.421 $FPR_{3\to4}$:0.597 ScFPR : 0.234
24	**de Ledinghen 2008** [4]	2008	Spain	English	Liver clinic	Clinical	C-S/R	656	656	LSM	METAVIR	$FPR_{0\to1}$:0.045 $FPR_{1\to2}$:0.051 $FPR_{2\to3}$:0.109 $FPR_{3\to4}$:0.157 ScFPR : 0.053
25	**Nunnari 2010** [5]	2010	Italy	English	Infectious diseases	Clinical	C-S/R	70	70	LB	METAVIR	$FPR_{0\to1}$:0.157 $FPR_{1\to2}$:0.280 $FPR_{2\to3}$:0.174 $FPR_{3\to4}$:0.099 ScFPR : 0.173

Supplementary Table 7 continued

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Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
26	**Mazzocato 2014** [6]	2014	Italy	English	Infectious diseases	Clinical	C-S/R	115	115	LSM	METAVIR	$FPR_{0\to1}$:0.172 $FPR_{1\to2}$:0.192 $FPR_{2\to3}$:0.658 $FPR_{3\to4}$:0.905 ScFPR : 0.216
27	**Suarez-Zarracina 2012** [7]	2012	Spain	English	Infectious diseases	Clinical	C-S/R	68	68	LSM	METAVIR	$FPR_{0\to1}$:0.079 $FPR_{1\to2}$:0.138 $FPR_{2\to3}$:0.124 $FPR_{3\to4}$:0.082 ScFPR : 0.095
28	**White 2012** [21]	2012	USA	English	Liver clinic	Clinical	R-P	308	308	FibroSURE-ActiTest	METAVIR	$FPR_{0\to1}$:0.078 $FPR_{1\to2}$:0.103 $FPR_{2\to3}$:0.092 $FPR_{3\to4}$:0.069 ScFPR : 0.078
29	**Reggiardo 2012** [22]	2012	Argentina	English	Blood transfusion	Non-clinical	R-P	40	40	LB	METAVIR	$FPR_{0\to1}$:0.075 $FPR_{1\to2}$:0.050 $FPR_{2\to3}$:0.128 $FPR_{3\to4}$:0.017 ScFPR : 0.066
30	**Liu 2014** [8]	2014	China	Chinese	Blood transfusion	Clinical	C-S/R	96	52	LSM	METAVIR	$FPR_{0\to1}$: 0.106 $FPR_{1\to2}$: 0.077 $FPR_{2\to3}$:0.154 $FPR_{3\to4}$:0.195 ScFPR : 0.101
31a	**Terrault 2008** [23]	2008	USA	English	Liver clinic	Clinical	R-P	157	157	LB	Ishak	$FPR_{0\to1}$:0.099 $FPR_{1\to2}$:0.080 $FPR_{2\to3}$:0.093 $FPR_{3\to4}$:0.030 ScFPR : 0.081
31b	**Terrault 2008** [23]	2008	USA	English	Liver clinic	Clinical	R-P	143	143	LB	Ishak	$FPR_{0\to1}$:0.100 $FPR_{1\to2}$:0.076 $FPR_{2\to3}$:0.076 $FPR_{3\to4}$:0.017 ScFPR : 0.079
32	**Guyader 2007** [24]	2007	France	English	Liver clinic	Clinical	R-P	586	580	LB	METAVIR	$FPR_{0\to1}$:0.075 $FPR_{1\to2}$:0.085 $FPR_{2\to3}$:0.136 $FPR_{3\to4}$: 0.221 ScFPR : 0.085
33	**Pradat 2007** [25]	2007	France	English	Liver clinic	Clinical	R-P	247	247	LB	METAVIR	$FPR_{0\to1}$:0.237 $FPR_{1\to2}$:0.094 $FPR_{2\to3}$:0.149 $FPR_{3\to4}$:0.064 ScFPR : 0.138

Supplementary Table 7 continued

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Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates
34a	**Castera 2004** [26]	2004	France	English	Liver clinic	Clinical	R-P	37	37	LB	METAVIR	FPR $_{0\to1}$:0.116 FPR $_{1\to2}$:0.176 FPR $_{2\to3}$:0.110 FPR $_{3\to4}$:0.218 ScFPR : 0.131
34b	**Castera 2004** [26]	2004	France	English	Liver clinic	Clinical	R-P	114	114	LB	METAVIR	FPR $_{0\to1}$:0.080 FPR $_{1\to2}$:0.111 FPR $_{2\to3}$:0.084 FPR $_{3\to4}$:0.175 ScFPR : 0.090
35a	**Mathurin 1998** [27]	1998	France	English	Liver clinic	Clinical	R-P	102	67	LB	METAVIR	FPR $_{0\to1}$:0.081 FPR $_{1\to2}$:0.034 FPR $_{2\to3}$:0.108 FPR $_{3\to4}$:0.281 ScFPR : 0.067
35b	**Mathurin 1998** [27]	1998	France	English	Liver clinic	Clinical	R-P	102	101	LB	METAVIR	FPR $_{0\to1}$:0.200 FPR $_{1\to2}$:0.098 FPR $_{2\to3}$:0.077 FPR $_{3\to4}$:0.201 ScFPR : 0.129
36	**Bruden 2017**[45]	2017	USA	English	Community	Non-clinical	R-P	407	407	LB	Ishak	FPR $_{0\to1}$:0.091 FPR $_{1\to2}$:0.153 FPR $_{2\to3}$:0.088 FPR $_{3\to4}$:0.062 ScFPR : 0.994
37	**Cepeda 2016**[28]	2016	Indian	English	IDU	Non-clinical	R-P	281	281	LSM	METAVIR	FPR $_{0\to1}$:0.088 FPR $_{1\to2}$:0.138 FPR $_{2\to3}$:0.242 FPR $_{3\to4}$:0.225 ScFPR : 0.118
38	**Cepeda 2017**[29]	2017	USA	English	IDU	Non-clinical	R-P	964	964	LSM	METAVIR	FPR $_{0\to1}$:0.042 FPR $_{1\to2}$:0.053 FPR $_{2\to3}$:0.143 FPR $_{3\to4}$:0.113 ScFPR : 0.053
39	**Sakellariou 2014**[34]	2014	Greece	English	Dialysis patients	Clinical	R-P	61	58	LB	Ishak	FPR $_{0\to1}$:0.322 FPR $_{1\to2}$:0.0822 FPR $_{2\to3}$:0.803 FPR $_{3\to4}$:0.449 ScFPR : 0.238
40a	**Lemos 2007 A**[31]	2007	Brazil	English	Dialysis patients	Clinical	R-P	39	38	LB	Ludwig	FPR $_{0\to1}$:0.092 FPR $_{1\to2}$:0.154 FPR $_{2\to3}$:0.116 FPR $_{3\to4}$:0.100 ScFPR : 0.105

Supplementary Table 7 continued

Study ID	Study	Year	Country	Language	Population	Setting	Design	Study SS	Biopsy SS	Assessment Method	Scoring system	Progression rates

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40b	**Lemos 2007 B**[31]	2007	Brazil	English	Dialysis patients	Clinical	R-P	117	117	LB	Ludwig	FPR $_{0\to1}$:0.145 FPR $_{1\to2}$:0.100 FPR $_{2\to3}$:0.485 FPR $_{3\to4}$:0.192 ScFPR : 0.144
41	**Delladetsima 2013**[32]	2013	Greece	English	Renal transplant	Clinical	R-P	23	29	LB	Ishak	FPR $_{0\to1}$:0.220 FPR $_{1\to2}$:0.102 FPR $_{2\to3}$:0.504 FPR $_{3\to4}$:0.655 ScFPR : 0.196
42	**Besheer 2017**[33]	2017	Egypt	English	Liver clinic	Clinical	R-P	122	122	LB	METAVIR	FPR $_{0\to1}$:0.150 FPR $_{1\to2}$:0.136 FPR $_{2\to3}$:0.179 FPR $_{3\to4}$:0.127 ScFPR : 0.135
43	**Midgard 2017**[43]	2017	International	English	Injection drug users	Clinical	R-P	93	122	LB/LSM/APRI	METAVIR	FPR $_{0\to1}$:0.052 FPR $_{1\to2}$:0.058 FPR $_{2\to3}$:0.173 FPR $_{3\to4}$:0.121 ScFPR : 0.062
44	**Chen 2017**[44]	2017	Australia	English	Liver clinic	Clinical	R-P	131	122	LB	METAVIR	FPR $_{0\to1}$:0.068 FPR $_{1\to2}$:0.081 FPR $_{2\to3}$:0.150 FPR $_{3\to4}$:0.245 ScFPR : 0.081
45	**Valva 2014**[9]	2014	Argentina	English	Liver clinic	Clinical	C-S/R	32	122	LB	METAVIR	FPR $_{0\to1}$:0.093 FPR $_{1\to2}$:0.163 FPR $_{2\to3}$:0.092 FPR $_{3\to4}$:0.027 ScFPR : 0.098
Supplementary Table 7 continued												

Supplementary Table 3. Table summarizing study characteristics for all 45 studies identified by the updated systematic review. Note: Of these, only studies with subjects that were HCV RNA positive were included in the meta-analysis (RNA data provided in S4 Table). *Abbreviations: HCV: Hepatitis C virus; C-S/R: cross-sectional/retrospective; R-P: retrospective-prospective; LB: liver biopsy; LSM: liver stiffness measurement; FPR: fibrosis progression rate; scFPR: stage-constant annual fibrosis progression rate (assuming constant progression over F0 to F4).*

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S4 Table: Table summarizing patient characteristics for the 45 identified studies

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m^2)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
1	**Agostini 2007**	42.4	62.86	12.00	11.41	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 65.8 BT: 14.4 SP: 19.8	.	10.36	0.00	F0: 24.00 F1: 24.01 F2: 22.62 F3: 22.60 F4: 6.76	.
2	**Allison 2012**	43.1	50.81	25.00	.	100.00	3.32	GT1: 73.5 GT2: 16.8 GT3: 3.8 GT4: 1.1	IDU: 0.0 BT: 100 SP: 0.0	33.76	.	.	F0: 32.97 F1: 26.49 F2: 25.95 F3: 12.43 F4: 2.16	70.22
3	**Boonwaat 2010**	34.0	76.28	15.00	46.05	100.00	.	GT1: 22.9 GT2: 6.7 GT3: 23.7 GT4: 3.0	IDU: 62.0 BT: 2.2 SP: .	.	4.85	8.09	F0: 28.10 F1: 28.76 F2: 19.61 F3: 18.95 F4: 4.58	.
4	**Bourliere 2012**	47.2	61.91	21.00	5.91	100.00	.	GT1: 52.1 GT2: 12.3 GT3: 24.9 GT4: 8.1	IDU: 39.2 BT: 2.2 SP: .	24.40	5.18	1.11	F0: 8.36 F1: 25.08 F2: 31.72 F3: 17.78 F4: 17.06	.
5	**Contreras 2007**	43.5	46.88	10.32	35.94	.	.	GT1: . GT2: . GT3: . GT4: .	IDU: 0.0 BT: 100 SP: 0.0	.	.	0.00	F0: 31.25 F1: 23.44 F2: 29.69 F3: 10.94 F4: 4.69	68.58
6	**Delgado-Borego 2010**	14.8	51.00	12.00	0.00	100.00	.	GT1: 88.2 GT2: 3.9 GT3: 6.9 GT4: 1.0	IDU: 2.0 BT: 4.0 SP : 15.0	.	.	.	F0: 8.80 F1: 52.00 F2: 15.70 F3: 20.60 F4: 2.90	.
7	**Forestier 2012**	54.0	53.06	13.00	.	100.00	6.58	GT1: 84.7 GT2: 3.1 GT3: 9.2 GT4: 3.1	IDU: . BT: . SP: .	26.00	.	.	F0: 6.67 F1 :33.3 F2: 31.11 F3: 13.33 F4: 15.56	59.00

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Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m²)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
8	**Goodman 2008**	9.8	56.20	9.80	0.00	100.00	.	GT1: 82.6 GT2: 5.8 GT3: 10.7 GT4: .	IDU: 0.0 BT: 7.4 SP: 14.9	20.3	0.00	0.00	F0: 14.05 F1: 45.45 F2: 34.71 F3: 4.13 F4: 1.65	.
9	**Hui 2007**	53.7	82.93	38.00	.	100.00	5.81	GT1: 37.8 GT2: 7.3 GT3: 6.1 GT4: .	IDU: 43.9 BT: 34.2 SP: 22.0	27.94	0.00	0.00	F0: 28.30 F1: 30.19 F2: 13.21 F3: 13.21 F4: 15.09	33.49
10a	**Liu 2014 – M**	43.9	77.50	14.69	27.45	100.00	2.70	GT1: 81.2 GT2: 4.0 GT3: 14.9 GT4: 0.0	IDU: 74.0 BT: . SP: .	.	8.85	.	F0: 11.9 F1: 22.8 F2: 38.60 F3: 15.80 F4: 10.90	90.30
10b	**Liu 2014 - M**	46.7	67.60	18.01	11.64	100.00	2.31	GT1: 67.3 GT2: 9.5 GT3: 14.5 GT4: 6.2	IDU: 53.1 BT: . SP: .	.	1.09	.	F0: 7.30 F1: 26.9 F2: 37.8 F3: 6.40 F4: 11.60	98.00
11	**Nanda 2012**	59.0	0.00	30.00	.	100.00	.	GT1: 100 GT2: 0.0 GT3: 0.0 GT4: 0.0	IDU: . BT: 0.0 SP: .	25.30	.	.	F0: 50.00 F1: 25.00 F2: 10.00 F3: 5.00 F4: 10.00	.
12	**Rao 2012**	53.7	44.83	25.20	21.26	100.00	6.22	GT1: 75.6 GT2: 11.2 GT3: . GT4: .	IDU: 0.0 BT: 100 SP: 0.0	.	0.00	1.44	F0: 25.71 F1: 25.14 F2: 17.71 F3: 14.29 F4: 17.14	45.80
13a	**Siddiqui 2008**	50.0	56.61	22.50	.	84.00	.	GT1: 57.5 GT2: 3.2 GT3: 0.9 GT4: 0.4	IDU:52.6 BT: 14.2 SP: 20.3	.	.	2.80	F0: 17.74 F1: 27.16 F2: 17.84 F3: 15.66 F4: 21.61	66.00
13b	**Siddiqui 2008**	45.3	60.55	22.50	.	82.00	.	GT1: 42.5 GT2: 6.5 GT3: 9.9 GT4: 1.3	IDU: 45.3 BT: 16.9 SP : 25.3	.	.	3.41	F0: 18.26 F1: 23.31 F2: 17.42 F3: 13.20 F4: 27.81	77.00

Supplementary Table 8 continued

Supplementary Materials

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m²)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
14	**Werner 2010**	49.1	72.73	4.43	.	100.00	6.12	GT1: 72.7 GT2: 13.6 GT3: 13.6 GT4: 0.0	IDU: . BT: . SP: .	.	.	.	F0: 27.27 F1: 40.91 F2: 18.18 F3: 9.09 F4:4.55	.
15a	**Bochud 2009**	42.0	60.00	21.00	55.02	100.00	6.00	GT1: 100 GT2: 0.0 GT3: 0.0 GT4: 0.0	IDU: 49.0 BT: 22.0 SP: .	23.90	7.00	0.00	F0: 14.0 F1: 37.0 F2: 27.0 F3: 11.0 F4: 11.0	66.00
15b	**Bochud 2009**	54.0	48.00	24.00	37.78	100.00	5.93	GT1: 0.0 GT2: 100 GT3: 0.0 GT4: 0.0	IDU:11.0 BT: 53.0 SP: .	24.90	2.00	0.00	F0: 14.00 F1: 27.00 F2: 31.00 F3: 16.00 F4: 12.00	45.00
15c	**Bochud 2009**	40.0	65.00	20.00	63.14	100.00	5.90	GT1: 0.0 GT2: 0.0 GT3: 100 GT4: 0.0	IDU:66.0 BT: 9.0 SP: .	23.30	7.00	0.00	F0: 10.00 F1: 28.00 F2: 32.00 F3: 11.00 F4: 19.00	76.00
15d	**Bochud 2009**	41.0	66.00	22.00	56.41	100.00	5.80	GT1: 0.0 GT2: 0.0 GT3: 0.0 GT4: 100	IDU: 60.0 BT: 11.0 SP: .	23.70	7.00	0.00	F0: 17.00 F1: 32.00 F2: 26.00 F3: 10.00 F4: 15.00	63.00
16	**Hissar 2009**	41.6	65.26	12.10	0.00	100.00	4.80	GT1: 11.7 GT2: . GT3: 49.3 GT4: 4.7	IDU: 0.5 BT: 76.1 SP: .	.	0.00	0.00	F0: 4.69 F1: 25.35 F2: 23.94 F3: 24.88 F4: 21.13	118.50
17	**Kallwitz 2010**	49.6	61.00	26.50	.	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 36.5 BT: 33.5 SP: .	30.10	0.00	0.00	F0: 10.0 F1: 10.0 F2: 22.50 F3: 22.50 F4: 35.00	.
18	**Kielland 2014**	37.3	74.5	17.75	.	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 100 BT: 0.0 SP: 0.0	.	0.98	4.90	F0: 11.48 F1: 68.85 F2: 3.28 F3: 4.92 F4: 11.48	.

Supplementary Table 8 continued

Supplementary Materials

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m²)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
19a	**Larsen 2010**	39.0	75.00	18.00	42.62	100.00	.	GT1: 0.0 GT2: 0.0 GT3: 100 GT4: 0.0	IDU: . BT: . SP: .	.	4.36	1.95	F0: 6.31 F1: 34.34 F2: 28.28 F3: 15.66 F4: 15.40	.
19b	**Larsen 2010**	40.0	75.00	19.00	43.61	100.00	.	GT1: 77.5 GT2: 5.9 GT3: 0.0 GT4: 16.4	IDU: . BT: . SP: .	.	7.05	2.06	F0: 8.30 F1: 46.62 F2: 27.05 F3: 9.63 F4: 8.40	.
20a	**Lawson 2010**	36.0	47.00	14.00	35.63	100.00	.	GT1: 29.9 GT2: 8.1 GT3: 26.4 GT4: .	IDU: 74.7 BT: 12.6 SP: .	22.70	0.00	0.00	F0: 58.32 F1: 25.35 F2: 7.61 F3: 2.54 F4: 5.07	.
20b	**Lawson 2010**	36.0	71.00	14.00	40.44	100.00	.	GT1: 30.9 GT2: 6.1 GT3: 33.8 GT4: .	IDU: 65.4 BT: 11.4 SP: .	25.00	0.00	3.16	F0: 37.02 F1: 22.01 F2: 10.01 F3: 13.95 F4: 17.00	.
21	**Marabita 2011**	47.0	52.23	25.00	0.00	100.00	.	GT1: 52.2 GT2: 30.0 GT3: 13.8 GT4: 4.1	IDU: 23.5 BT: 74.9 SP: .	25.30	0.00	0.00	F0: 0.81 F1: 30.36 F2: 32.39 F3: 20.24 F4: 16.19	.
22a	**Patin 2012-French coh.**	48.2	44.75	20.17	14.56	.	.	GT1: 63.0 GT2: 8.8 GT3: 16.1 GT4: 2.1	IDU: 33.6 BT: 43.9 SP: .	.	0.00	0.00	F0: 8.78 F1: 52.25 F2: 4.28 F3: 19.91 F4: 14.78	.
22b	**Patin 2012-Swiss coh.**	43.6	62.39	22.39	19.02	.	.	GT1: 52.2 GT2: 9.7 GT3: 27.8 GT4: 6.8	IDU: 41.8 BT: 19.2 SP : .	.	0.00	0.00	F0: 12.54 F1: 35.34 F2: 31.27 F3: 0.98 F4: 19.87	.
22c	**Patin 2012-US/France**	48.0	60.31	23.48	11.88	100.00	.	GT1: 67.2 GT2: 5.3 GT3: 16.9 GT4: 4.4	IDU: 7.8 BT: 4.7 SP : .	.	0.00	0.00	F0: 12.81 F1: 35.63 F2: 21.88 F3: 19.06 F4: 10.63	.

Supplementary Table 8 continued

Supplementary Materials

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m²)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
22d	**Patin 2012-International**	45.8	40.65	16.96	.	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 20.6 BT: 5.1 SP : .	.	0.00	0.00	F0: 17.45 F1: 38.47 F2: 25.23 F3: 10.12 F4: 8.72	.
22e	**Patin 2012-Australian**	62.4	70.78	20.20	.	100.00	.	GT1: 100 GT2: 0.0 GT3: 0.0 GT4: 0.0	IDU: 0 BT: 0 SP : .	.	0.00	0.00	F0: 5.94 F1: 29.68 F2: 33.33 F3: 14.61 F4: 16.44	.
23	**Brescini 2014**	45.0	62.37	6.25	15.05	.	5.76	GT1: 48.9 GT2: 12.4 GT3: 24.7 GT4: 4.3	IDU: 47.9 BT: . SP: .	.	0.00	0.00	F0: 30.11 F1: 30.65 F2: 16.13 F3: 9.14 F4: 13.98	58.00
24	**de Ledinghen 2008**	52.8	38.41	23.50	0.00	100.00	5.83	GT1: 60.4 GT2: 20.1 GT3: 8.8 GT4: 9.5	IDU:16.0 BT: 33.8 SP : .	.	0.00	0.00	F0: 34.60 F1: 34.45 F2: 13.41 F3: 7.16 F4: 10.37	59.00
25	**Nunnari 2010**	52.5	57.14	12.40	.	100.00	2.80	GT1: 71.4 GT2: 14.3 GT3: 14.3 GT4: 0.0	IDU: . BT: . SP : .	.	0.00	0.00	F0: 14.29 F1: 14.29 F2: 28.57 F3: 28.57 F4: 14.29	97.40
26	**Mazzocato 2014**	48.0	58.26	6.00	18.26	.	.	GT1: 38.3 GT2: 18.3 GT3: 13.9 GT4: 2.6	IDU:32.2 BT: . SP: .	.	0.00	0.00	F0: 35.65 F1: 34.78 F2: 9.57 F3: 4.35 F4: 15.65	56.00
27	**Suarez-Zarracina 2012**	46.5	61.76	23.00	64.71	100.00	5.87	GT1: 82.4 GT2: 1.5 GT3: 11.8 GT4: 2.9	IDU: 48.5 BT: 50.0 SP: 0.0	.	0.00	0.00	F0: 16.18 F1: 16.18 F2: 22.06 F3: 25.00 F4: 20.59	85.50
28	**White 2012**	57.0	100.00	34.00	34.09	99.35	6.35	GT1: 85.7 GT2: 8.4 GT3: 4.5 GT4: 0.6	IDU: 50.7 BT: 17.5 SP: .	.	0.00	0.00	F0: 7.14 F1: 12.66 F2: 21.43 F3: 26.95 F4: 31.82	.

Supplementary Table 8 continued

Supplementary Materials

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m²)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
29	**Reggiardo 2012**	52.5	37.50	21.50	32.50	100	.	GT1: 50.0 GT2: 37.5 GT3: 12.5 GT4: 0.0	IDU: 0.0 BT: 100 SP: 0.0	.	0.00	0.00	F0: 20.00 F1: 42.50 F2: 15.00 F3: 20.00 F4: 2.50	.
30	**Liu 2014**	33.6	43.75	10.22	.	.	6.22	GT1: 69.8 GT2: . GT3: . GT4: .	IDU: 0.0 BT: 100 SP : 0.0	.	.	1.04	F0: 33.65 F1: 42.31 F2: 13.46 F3: 5.77 F4: 3.85	116.00
31a	**Terrault 2008**	46.6	64.33	25.50	0.00	100.00	.	GT1: 100 GT2: 0.0 GT3: 0.0 GT4: 0.0	IDU: 61.8 BT: 26.8 SP: 0.0	.	0.00	0.00	F0: 8.00 F1: 26.00 F2: 25.50 F3: 31.00 F4: 9.00	110.40
31b	**Terrault 2008**	47.9	66.43	24.00	0.00	100.00	.	GT1: 100 GT2: 0.0 GT3: 0.0 GT4: 0.0	IDU: 57.3 BT: 23.1 SP : 0.0	.	0.00	0.00	F0: 9.00 F1: 29.50 F2: 29.50 F3: 28.00 F4: 4.00	66.00
32	**Guyader 2007**	41.6	58.00	16.00	36.00	100.00	.	GT1: 39.5 GT2: 6.8 GT3: 15.0 GT4:.	IDU: 33.0 BT: 34.0 SP : 33.0	23.00	0.00	0.00	F0: 30.00 F1: 33.00 F2: 17.00 F3: 8.00 F4: 11.00	.
33	**Pradat 2007**	39.5	63.97	14.50	15.38	100.00	.	GT1: 35.6 GT2: . GT3: . GT4: .	IDU: . BT: . SP : .	.	.	.	F0: 3.24 F1: 37.25 F2: 25.10 F3: 25.51 F4: 8.91	.
34a	**Castera 2004**	34.4	83.78	12.10	.	100.00	9.30	GT1: 0.0 GT2: 0.0 GT3: 100 GT4: 0.0	IDU: 65.0 BT: 16.0 SP: 19.0	18.10	0.00	0.00	F0: 24.50 F1: 24.50 F2: 30.0 F3: 10.50 F4: 10.50	118.00
34b	**Castera 2004**	45.7	70.18	15.60	.	100.00	6.10	GT1: 78.9 GT2: 15.0 GT3: 0.0 GT4: 3.1	IDU: 14.0 BT: 41.0 SP: 45.0	32.90	0.00	0.00	F0: 28.50 F1: 28.50 F2: 26.0 F3: 8.50 F4: 8.50	143.00

Supplementary Table 8 continued

Supplementary Materials

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m²)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
35a	**Mathurin 1998**	43.0	40.20	14.90	10.78	65.00	.	GT1: 43.1 GT2: 7.8 GT3: 4.9 GT4: 1.0	IDU: 32.0 BT: 35.0 SP: .	.	0.00	0.00	F0: 29.85 F1: 52.24 F2: 10.45 F3: 2.99 F4: 4.48	24.50
35b	**Mathurin 1998**	44.0	40.20	14.10	10.78	80.00	.	GT1: 45.1 GT2: 4.9 GT3: 11.8 GT4: 3.9	IDU: 31.0 BT: 40.0 SP: .	.	0.00	0.00	F0: 5.94 F1: 37.62 F2: 35.64 F3: 9.00 F4: 10.89	140.00
36	**Bruden, 2017**	41.2	4864	18.60	8.85	100.00	.	GT1:68.80 GT2:14.74 GT3:13.27 GT4: 0.41	IDU: 58.7 BT: 14.0 SP: 27.3	.	0.00	0.00	F0: 18.43 F1: 18.42 F2: 32.19 F3: 21.62 F4: 9.34	.
37	**Cepeda, 2016**	41.6	100.00	16.90	67.97	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 100 BT: 0.0 SP: 0.0	19.80	30.25	4.62	F0: 22.42 F1: 22.78 F2: 14.23 F3: 14.23 F4: 26.33	49.00
38	**Cepeda, 2017**	49.0	71.58	27.50	26.21	100.00	6.40	GT1: . GT2: . GT3: . GT4: .	IDU: 100 BT: 0.0 SP: 0.0	.	34.96	.	F0: 31.33 F1: 31.33 F2: 11.31 F3: 11.31 F4: 14.73	.
39	**Sakellariou, 2014**	45.7	60.66	4.20	0.00	100.00	5.06	GT1: 27.9 GT2: 1.6 GT3: 23.0 GT4: 14.8	IDU: . BT: . SP: .	.	0.00	0.00	F0: 25.86 F1: 60.34 F2: 5.17 F3: 5.17 F4: 3.45	.
40a	**Lemos, 2007 A**	57.0	64.10	22.00	0.00	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 0 .0 BT: 69.2 SP: 0.0	.	0.00	0.00	F0: 12.82 F1: 14.10 F2: 24.36 F3: 23.08 F4: 23.10	.
40b	**Lemos, 2007 B**	45.0	62.39	6.00	0.00	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 0.0 BT: 25.6 SP: 0.0	.	0.00	0.00	F0: 41.88 F1: 41.88 F2: 6.84 F3: 6.84 F4: 2.6	.

Supplementary Table 8 continued

Supplementary Materials

Study ID	Study	Age (yrs)	Gender (%Male)	DOI (yrs)	**Excess alcohol use (%)	HCV RNA+ (%)	HCV RNA load (log 10 IU/ml)	Genotype (%)	Mode of Infection (%)	BMI (kg/m²)	HIV (%)	HBV (%)	METAVIR (%)	Mean ALT (IU/L)
41	**Delladetsima, 2013**	42.7	60.87	4.40	.	87.00	3.50	GT1: 47.8 GT2: 0.0 GT3: 26.1 GT4: 13.0	IDU: . BT: . SP: .	.	.	.	F0: 47.83 F1: 60.87 F2: 8.70 F3: 4.35 F4: 4.35	.
42	**Besheer, 2017**	49.5	63.11	19.00	.	100.00	5.79	GT1: . GT2: . GT3: . GT4: .	IDU: . BT: . SP: .	.	.	.	F0: 5.73 F1: 18.85 F2: 19.67 F3: 25.41 F4: 30.33	55.50
43	**Midgard, 2017**	41.0	82.80	21.00	16.13	100.00	.	GT1: . GT2: . GT3: . GT4: .	IDU: 100 BT: 0.0 SP: 0.0	.	0.00	0.00	F0: 33.33 F1: 34.41 F2: 10.75 F3: 10.75 F4: 10.75	.
44	**Chen, 2017**	37.0	69.47	17.00	.	100.00	6.10	GT1: . GT2: . GT3: . GT4: .	IDU:31.3 BT: 16.8 SP: 18.3	25.20	0.00	0.00	F0: 31.30 F1: 32.82 F2: 15.27 F3: 7.63 F4: 12.98	94.00
45	**Valva, 2014**	51.0	65.63	20.00	.	100.00	5.74	GT1: . GT2: . GT3: . GT4: .	IDU: 21.9 BT: 12.5 SP: 62.5	.	0.00	0.00	F0: 15.63 F1: 15.63 F2: 31.25 F3: 31.25 F4: 6.25	67.00
Supplementary Table 8 continued														

Supplementary Table 4. Table summarizing patient characteristics for all 45 studies identified by the updated systematic review. Note: Of these, only studies with subjects that were HCV RNA positive were included in the meta-analysis. *Abbreviations: HCV: Hepatitis C virus; DOI: duration of infection; ALT: alanine aminotransferase; BMI: body mass index; HIV: human immunodeficiency virus; HBV: hepatitis B virus; GT: genotype BT: blood transfusion; IDU: intravenous drug use; SP: sporadic risk.*

S5 Table: Summary of subgroups excluded from the meta-analysis

	All Groups		Original Groups		New Groups	
	N	**SS**	**N**	**SS**	**N**	**SS**
All groups	40	15,117	30	7,629	10	7,488
Study Setting						
Clinical	35	9,772	27	6,426	8	3,346
Non-Clinical	5	5,345	3	1,203	2	4,142
Study Design						
Cross-sectional/Retrospective	32	10,258	28	7,447	4	2,811
Retrospective-Prospective	8	4,859	2	182	6	4,677
Study population						
Females	.	.	.	.	.	.
Blood donors	1	348	.	.	1	348
Post-transfusion	2	161	1	65	1	96
Liver Clinic	23	9,659	18	6,496	5	3,163
Injection drug users	2	432	2	432	.	.
Community	2	3,866	1	72	1	3,794
Pediatric patients	4	374	4	374	.	.
Renal transplant recipients	2	68	1	45	1	23
Dialysis patients	4	209	3	145	1	64
Infectious diseases	.	.	.	.	.	.
Publication year						
<2000	8	2,749	6	2,545	2	204
2000 to <2005	19	4,037	19	4,037	.	.
2005 to<2010	9	7,556	5	1,047	4	6,509
≥2010	4	775	0	.	4	775
Age at assessment						
Age<40	32	6,435	22	3,096	10	3,339
Age≥ 40	136	51,119	89	30,025	47	21,094
Age at infection						
<20 years	16	2,757	9	1,101	7	1,656
30 to <40 years	113	41,987	77	24,254	36	17,733
20 to <30 years	33	12,225	25	7,766	8	4,459
≥40 years	6	585	0	.	6	585
Estimated duration of infection						
<10 years	14	1,244	7	599	7	645
10 to <20 years	94	31,836	69	19,660	25	12,176
≥ 20 years	60	24,474	35	12,862	25	11,612
Viral Genotype						
Genotype 1	10	3,000	5	1,854	5	1,146
Genotype 2	1	90	0	.	1	90
Genotype 3	3	1,426	0	.	3	1,426
Genotype 4	1	117	0	.	1	117

Supplemental Table 5. Summary of subgroups excluded from the meta-analysis. 40 study groups (30 from the original review and 10 update) were excluded from the meta-analysis due to incomplete or missing assessment of RNA status for all study subjects. *Abbreviations: N: number of groups included in the meta-analysis; SS: total sample size in each group.; CHC: chronic hepatitis C.*

Supplementary Materials

S6 Table: Summary of clinical characteristics of study subjects stratified by review update

	Updated Review (1990-2018)			Original Review (1990-2007)			New Groups (2007-2018)		
	N	**Mean**	**SE**	N	**Mean**	**SE**	N	**Mean**	**SE**
Sample size	131	326	35.9	81	315	43.4	50	344	63.1
Male (%)	131	62.0	1.5	81	62.1	2.0	50	61.9	2.1
Age at assessment (yrs.)	131	44.3	0.6	81	44.3	0.5	50	44.4	1.3
Estimated age at infection (yrs.)	131	25.8	0.5	81	25.8	0.4	50	25.8	1.3
Estimated duration of infection (yrs.)	131	18.4	0.5	81	18.5	0.5	50	18.2	1.0
Cirrhosis (%)	131	12.0	0.7	81	11.3	0.8	50	13.2	1.2
Steatosis (%)	39	50.3	3.9	21	48.9	4.4	18	52	6.8
BMI (kg/m^2)	49	25.7	0.4	30	26.1	0.4	19	25	0.9
HIV (%)	106	2.0	0.7	63	1.5	0.8	43	2.8	1.1
HBV (HBsAg positive, %)	104	0.4	0.1	64	0.3	0.1	40	0.6	0.3
Elevated ALT (%)	52	76.2	4.0	37	80.8	4.0	15	65	9.2
ALT (IU/L)	58	87.5	4.3	35	94.3	5.9	23	77.3	5.7
Excess alcohol use (%)	102	19.9	2.1	67	18.1	2.5	35	23.2	3.7
Mode of infection									
IDU (%)	110	43.4	2.5	68	43	2.8	42	44.1	5.0
BT (%)	107	25.7	2.0	68	27.1	2.1	39	23.4	4.0
Sporadic (%)	90	22.4	2.0	68	25.4	2.3	22	13.2	3.8
HCV RNA load (log_{10}IU/mL)	49	5.8	0.2	27	6.1	0.2	22	5.5	0.3
Genotype									
Genotype 1 (%)	113	56.2	2.4	71	57.2	2.4	42	54.5	4.9
Genotype 2 (%)	89	9.5	1.3	49	8.7	0.9	40	10.4	2.6
Genotype 3 (%)	95	17.6	2.0	54	15	1.3	41	21.1	4.3
Genotype 4 (%)	70	4.6	1.5	34	3.4	0.7	36	5.7	2.8
Racial groups									
White (%)	68	68.6	4.3	34	67.2	5.2	34	70	6.9
Black (%)	54	13.4	3.4	30	15.7	4.4	24	10.5	5.5
Asian (%)	47	5.4	3.0	24	5.7	4.1	23	5.1	4.3

Supplementary Table 6. Summary of clinical characteristics of study subjects included in the meta-analysis stratified by review update. Meta-analysis was restricted to study groups where all subjects were confirmed by HCV RNA testing (N=131). *Abbreviations: BMI: body mass index; ALT: alanine aminotransferase; IDU: injection drug use; BT: blood transfusion: HCV: hepatitis C virus; HIV: human immunodeficiency virus; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; RNA: ribonucleic acid; N: number of groups in meta-analysis reporting parameter; SE: standard error.*

Supplementary Materials

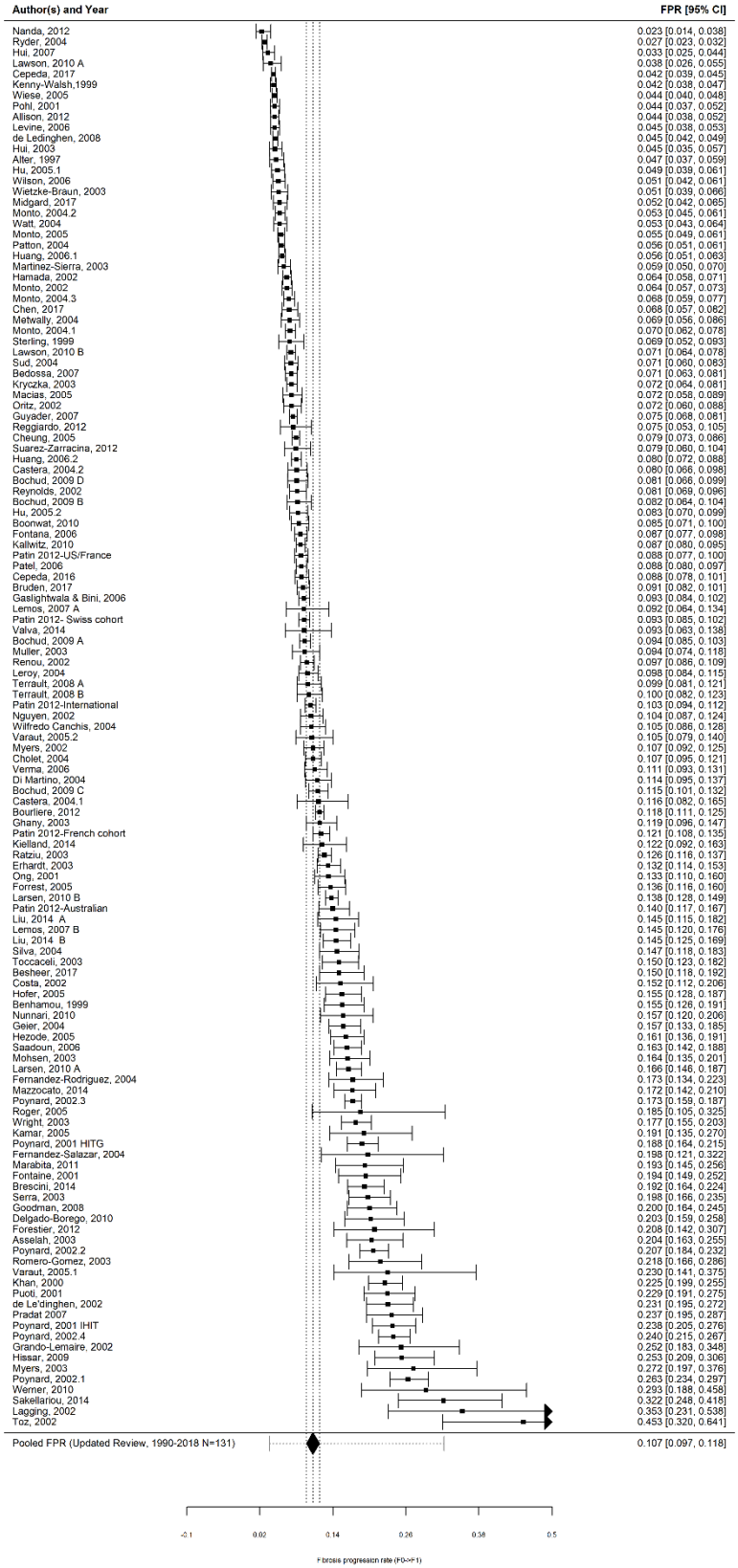
S7 Table: Hepatic fibrosis progression rates stratified by review update

	Updated Review (1990-2018)					Original Review (1990-2007)				
	N	Mean	95% CI		I^2	N	Mean	95% CI		I^2
[1] All identified groups										
F0 → F1	171	0.112	0.103	0.122	98%	111	0.117	0.104	0.130	98%
F1 → F2	171	0.088	0.080	0.097	98%	111	0.085	0.075	0.096	98%
F2 → F3	171	0.123	0.113	0.133	94%	111	0.120	0.109	0.133	91%
F3 → F4	171	0.120	0.108	0.132	89%	111	0.116	0.104	0.129	83%
scFPR	171	0.099	0.093	0.104	85%	111	0.103	0.098	0.108	85%
[2] HCV RNA+ groups										
F0 → F1	131	0.107	0.097	0.118	98%	81	0.108	0.095	0.123	98%
F1 → F2	131	0.082	0.074	0.091	97%	81	0.076	0.066	0.087	98%
F2 → F3	131	0.117	0.107	0.129	94%	81	0.111	0.099	0.124	89%
F3 → F4	131	0.116	0.104	0.131	89%	81	0.111	0.098	0.125	83%
scFPR	131	0.094	0.088	0.100	85%	81	0.091	0.084	0.098	83%

Supplementary Table 7. Annual stage-specific and stage-constant fibrosis progression rates based on random effect meta-analyses of [1] all identified study groups meeting inclusion/exclusion criteria (N=171); or [2] subset of identified groups where CHC was confirmed by HCV RNA testing in all subjects (N=131) stratified by review update. Hepatic fibrosis stages were based on METAVIR fibrosis scoring system. *Abbreviations: CHC: chronic hepatitis C; scFPR: stage-constant annual fibrosis progression rate (assuming constant progression over F0 to F4); I^2: indicates the percentage of variability in estimates due to heterogeneity vs. sampling error; N: number of groups included in the meta-analyses.*

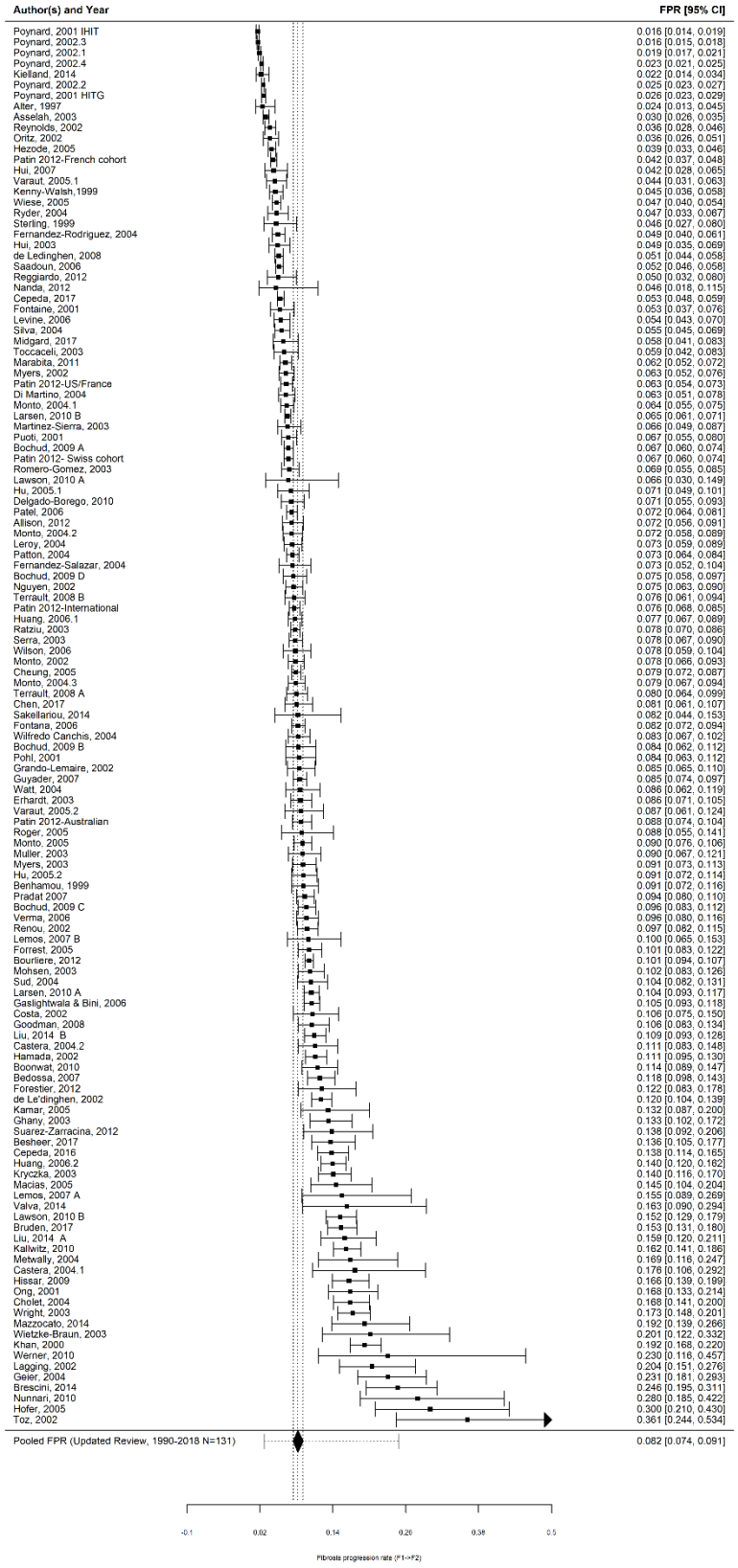
Supplementary Materials

S2 Figure: Forrest plot for fibrosis progression rate from F0 to F1



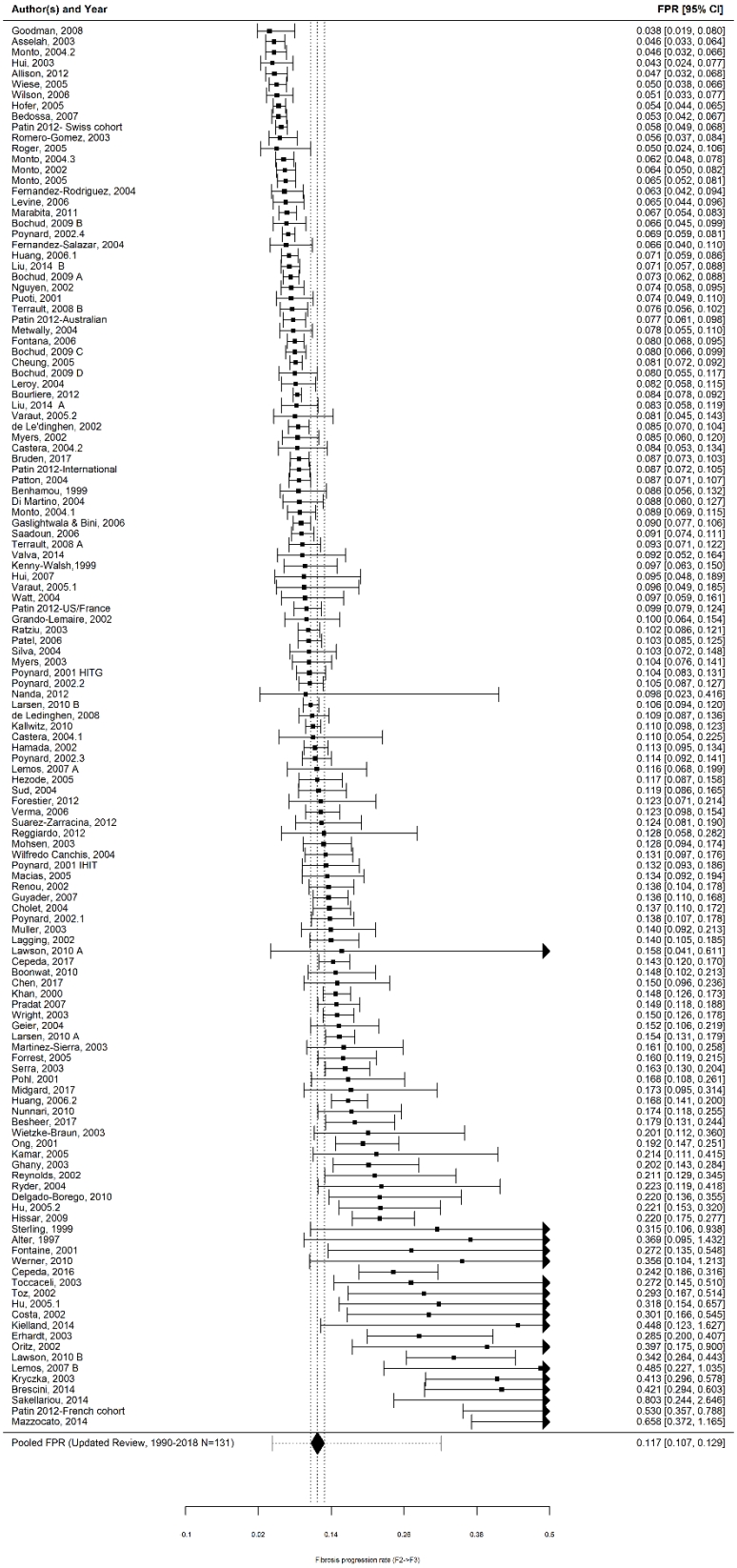
Supplementary Materials

S3 Figure: Forrest plot for fibrosis progression rate from F1 to F2



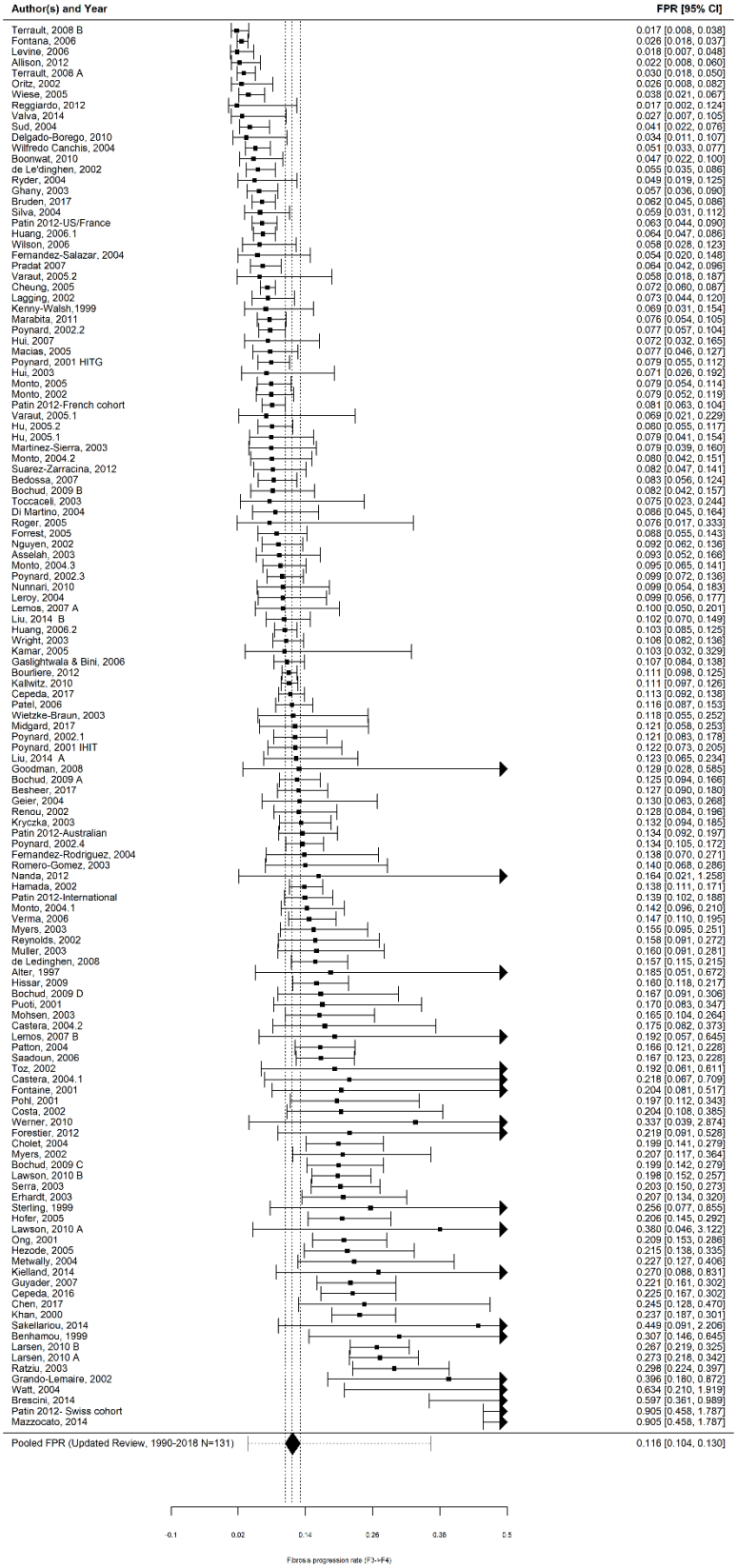
Supplementary Materials

S4 Figure: Forrest plot for fibrosis progression rate from F2 to F3



Supplementary Materials

S5 Figure: Forrest plot for fibrosis progression rate from F3 to F4



Supplementary Materials

S8 Table: Covariate-adjusted hepatic fibrosis progression rates for CHC subgroups

	F0 → F1			F1 → F2			F2 → F3			F3 → F4			scFPR			TTC* (yrs)
	Mean	95%CI		Mean	95%CI		Mean	95%CI		Mean	95%CI		Mean	95%CI		
All groups	0.107	0.099	0.115	0.082	0.075	0.090	0.119	0.110	0.129	0.116	0.105	0.129	0.096	0.092	0.100	38
Study design																
Cross-sectional/Retrospective	0.110	0.100	0.122	0.081	0.072	0.092	0.119	0.107	0.132	0.115	0.100	0.132	0.096	0.091	0.101	39
Retrospective-Prospective	0.101	0.086	0.118	0.084	0.069	0.103	0.119	0.100	0.141	0.120	0.097	0.148	0.097	0.089	0.105	39
Study population**																
Females	0.063	0.039	0.103	0.073	0.040	0.136	0.115	0.067	0.199	0.071	0.035	0.144	0.076	0.058	0.100	52
Blood donors	0.102	0.059	0.176	0.060	0.030	0.120	0.088	0.047	0.166	0.059	0.025	0.138	0.081	0.058	0.114	55
Pediatric patients	0.233	0.119	0.459	0.094	0.041	0.218	0.114	0.051	0.254	0.080	0.023	0.283	0.151	0.093	0.245	36
Post transfusion	0.131	0.056	0.305	0.085	0.030	0.247	0.125	0.046	0.341	0.062	0.015	0.247	0.116	0.066	0.204	44
Liver clinic	0.106	0.096	0.117	0.083	0.073	0.095	0.116	0.104	0.129	0.119	0.104	0.136	0.096	0.091	0.100	38
Injection drug users	0.125	0.079	0.197	0.053	0.030	0.094	0.116	0.069	0.193	0.206	0.111	0.380	0.095	0.076	0.120	40
Community	0.133	0.085	0.207	0.098	0.057	0.171	0.118	0.076	0.183	0.145	0.086	0.242	0.109	0.091	0.130	33
Dialysis patients	0.094	0.061	0.144	0.048	0.028	0.083	0.156	0.090	0.271	0.108	0.056	0.209	0.076	0.056	0.103	47
Renal transplant	0.105	0.063	0.174	0.108	0.057	0.203	0.124	0.067	0.228	0.082	0.034	0.202	0.112	0.076	0.164	39
Infectious diseases	0.082	0.049	0.137	0.114	0.059	0.219	0.151	0.086	0.266	0.147	0.075	0.291	0.095	0.071	0.126	34
Publication year																
<2000	0.070	0.042	0.117	0.064	0.034	0.123	0.112	0.059	0.213	0.199	0.091	0.437	0.073	0.052	0.101	44
2000 to <2005	0.106	0.092	0.121	0.073	0.061	0.086	0.112	0.097	0.129	0.115	0.096	0.137	0.091	0.085	0.097	41
2005 to <2010	0.115	0.099	0.135	0.092	0.076	0.112	0.112	0.095	0.131	0.110	0.090	0.134	0.100	0.092	0.107	38
≥2010	0.105	0.087	0.127	0.092	0.073	0.116	0.141	0.116	0.172	0.120	0.093	0.153	0.104	0.095	0.114	36
HCV genotype																
Genotype-1	0.127	0.104	0.155	0.069	0.054	0.089	0.098	0.080	0.121	0.098	0.076	0.126	0.093	0.084	0.102	43
Genotype non-1	0.082	0.062	0.108	0.102	0.071	0.144	0.160	0.120	0.215	0.139	0.097	0.199	0.099	0.086	0.113	35
Genotype-3	0.099	0.064	0.153	0.105	0.061	0.183	0.128	0.081	0.204	0.164	0.094	0.286	0.106	0.086	0.130	34
Genotype non-3	0.103	0.090	0.117	0.082	0.070	0.096	0.124	0.108	0.143	0.113	0.095	0.133	0.095	0.089	0.101	39
Race																
White	0.117	0.099	0.138	0.076	0.062	0.093	0.107	0.090	0.127	0.120	0.097	0.149	0.094	0.087	0.103	39
Black	0.074	0.044	0.122	0.110	0.059	0.207	0.146	0.086	0.248	0.062	0.032	0.122	0.096	0.075	0.123	46
Asian	0.109	0.052	0.227	0.103	0.041	0.261	0.148	0.062	0.353	0.295	0.098	0.891	0.107	0.067	0.172	29

Supplementary Table 8. Annual fibrosis progression rates adjusted for study design, population, publication year, age at HCV infection (mean: 26), duration of infection (mean: 17.6), male gender (mean: 62%), infection by IDU (mean: 43%), infection by blood transfusion (mean: 26%), excess alcohol consumption (mean: 18%), HIV positivity (mean: 2%), genotype-1 (mean: 56%), genotype-3 (mean:17%) and race (69% White; 13% Black and 5% Asian) except the following groups: † pediatric subgroup was adjusted for age at infection at 1.4 and duration of infection at 11 years; †† female subgroup was not adjusted by the mean gender (male gender: 0%); and *post-transfusion cohort was adjusted for the mode of infection by IDU at 0% and blood transfusion at 100%; IDU cohort was adjusted for the mode of infection by IDU at 100% and blood transfusion at 0%. *Abbreviations: scFPR: stage-constant annual fibrosis progression rate (assuming constant progression over F0 to F4); *TTC: time-to-cirrhosis (based on adjusted stage-specific annual progression rates); CHC: chronic hepatitis C; HCV: hepatitis C virus; IDU: Injection drug use.*

Supplementary Materials

S9 Table: Univariate random effects meta-regression of covariates associated with fibrosis progression

	F0→F1*				F1→F2*				F2→F3*				F3→F4*				scFPR*			
Predictors	**β**	**SE**	**P-value**	**RR**	**β**	**SE**	**P-value**	**RR**	**β**	**SE**	**P-value**	**RR**	**β**	**SE**	**P-value**	**RR**	**β**	**SE**	**P-value**	**RR**
Study setting																				
Clinical (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
Non-clinical	-0.383	0.132	**0.004**	***0.68***	-0.287	0.137	**0.039**	***0.75***	-0.055	0.134	0.683	*0.95*	-0.128	0.162	0.432	*0.88*	-0.221	0.085	**0.011**	***0.80***
Study design																				
Cross-sectional/Retrospective (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
Retrospective-Prospective	-0.206	0.105	0.051	*0.81*	-0.004	0.109	0.970	*1.00*	-0.057	0.104	0.585	*0.94*	-0.078	0.125	0.531	*0.92*	-0.102	0.066	0.128	*0.90*
Study population																				
Liver clinic (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
Females	-0.798	0.240	**0.001**	***0.45***	-0.467	0.252	0.067	*0.63*	-0.408	0.245	0.098	*0.67*	-0.779	0.313	**0.014**	***0.46***	-0.561	0.158	**0.001**	***0.57***
Blood donors	-0.458	0.304	0.135	*0.63*	-0.520	0.322	0.109	*0.59*	-0.209	0.329	0.526	*0.81*	-0.685	0.411	0.098	*0.50*	-0.355	0.214	0.099	*0.70*
Pediatric patients	0.642	0.371	0.086	*1.90*	0.064	0.379	0.866	*1.07*	-0.076	0.395	0.848	*0.93*	-0.643	0.598	0.284	*0.53*	0.365	0.283	0.199	*1.44*
Post-transfusion	-0.429	0.373	0.253	*0.65*	-0.055	0.387	0.887	*0.95*	0.066	0.376	0.861	*1.07*	-0.162	0.478	0.735	*0.85*	-0.171	0.242	0.480	*0.84*
Injecting drug users	0.026	0.172	0.881	*1.03*	-0.145	0.177	0.413	*0.87*	0.092	0.170	0.590	*1.10*	0.543	0.197	**0.007**	***1.72***	0.020	0.103	0.849	*1.02*
Community	0.235	0.262	0.372	*1.26*	0.073	0.266	0.785	*1.08*	0.011	0.242	0.963	*1.01*	0.170	0.274	0.537	*1.18*	0.122	0.142	0.390	*1.13*
Dialysis patients	0.132	0.224	0.557	*1.14*	-0.088	0.239	0.714	*0.92*	0.774	0.257	**0.003**	***2.17***	0.150	0.307	0.627	*1.16*	0.099	0.175	0.571	*1.10*
Renal transplant recipients	0.752	0.275	**0.007**	***2.12***	0.751	0.289	**0.010**	***2.12***	0.541	0.300	0.073	*1.72*	0.076	0.428	0.859	*1.08*	0.699	0.222	**0.002**	***2.01***
Infectious diseases	0.301	0.266	0.259	*1.35*	0.934	0.278	**0.001**	***2.54***	0.895	0.261	**0.001**	***2.45***	0.814	0.302	**0.008**	***2.26***	0.618	0.166	**<.001**	***1.86***
Publication year																				
<2000 (ref)	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*	_	_	_	*1.00*
2000 to <2005	0.562	0.290	0.055	*1.75*	0.453	0.305	0.139	*1.57*	-0.180	0.33	0.582	*0.84*	-0.357	0.385	0.355	*0.70*	0.328	0.213	0.126	*1.39*
2005 to <2010	0.352	0.295	0.234	*1.42*	0.568	0.309	0.069	*1.76*	-0.327	0.330	0.323	*0.72*	-0.630	0.389	0.108	*0.53*	0.238	0.216	0.272	*1.27*
≥2010	0.453	0.296	0.128	*1.57*	0.687	0.311	**0.029**	***1.99***	0.015	0.332	0.965	*1.01*	-0.227	0.392	0.563	*0.80*	0.398	0.217	0.069	*1.49*
Gender – male†	0.518	0.290	0.076	*1.68*	0.519	0.297	0.083	*1.68*	0.092	0.289	0.751	*1.10*	0.549	0.352	0.121	*1.73*	0.340	0.186	0.069	*1.41*
Age at assessment (yrs.)	-0.026	0.007	**0.001**	***0.97***	-0.0003	0.008	0.967	*1.00*	-0.012	0.007	0.103	*0.99*	-0.019	0.010	**0.050**	***0.98***	-0.017	0.005	**0.001**	***0.98***
Estimated Age at infection (yrs.)	0.023	0.008	**0.005**	***1.02***	0.029	0.008	**<.001**	***1.03***	0.035	0.008	**<.0001**	***1.04***	0.027	0.010	**0.009**	***1.03***	0.026	0.005	**<.0001**	***1.03***
Estimated Duration of infection (yrs.)	-0.065	0.007	**<.0001**	***0.94***	-0.036	0.009	**<.0001**	***0.96***	-0.059	0.008	**<.0001**	***0.94***	-0.058	0.010	**<.0001**	***0.94***	-0.052	0.004	**<.0001**	***0.95***
Injecting drug use†	0.022	0.204	0.913	*1.02*	-0.092	0.207	0.657	*0.91*	-0.180	0.199	0.369	*0.84*	0.500	0.236	**0.036**	***1.65***	-0.003	0.128	0.979	*1.00*
Blood transfusion†	0.417	0.273	0.129	*1.52*	0.284	0.279	0.311	*1.33*	0.551	0.263	**0.038**	*1.73*	0.188	0.321	0.559	*1.21*	0.362	0.169	**0.034**	***1.44***
Elevated ALT†	0.852	0.272	**0.002**	***2.34***	0.074	0.297	0.805	*1.08*	-0.058	0.305	0.851	*0.94*	0.332	0.369	0.370	*1.39*	0.476	0.199	**0.018**	***1.61***
Excess alcohol use†	-0.644	0.267	**0.017**	***0.53***	0.432	0.273	0.117	*1.54*	-0.035	0.261	0.893	*0.97*	0.275	0.305	0.368	*1.32*	-0.066	0.165	0.687	*0.94*
HIV positive†	-0.192	0.809	0.813	*0.83*	0.116	0.815	0.888	*1.12*	-0.365	0.770	0.636	*0.69*	1.052	0.909	0.249	*2.86*	-0.069	0.486	0.888	*0.93*
Genotype-1†	-0.080	0.214	0.708	*0.92*	-0.358	0.215	0.099	*0.70*	-0.626	0.199	**0.002**	***0.53***	-0.935	0.236	**<.001**	***0.39***	-0.317	0.129	**0.015**	***0.73***
Genotype-3†	0.378	0.300	0.210	*1.46*	0.259	0.307	0.401	*1.29*	0.376	0.290	0.198	*1.46*	0.962	0.337	**0.005**	***2.62***	0.367	0.184	**0.048**	***1.44***
White†	0.019	0.197	0.925	*1.02*	0.0004	0.201	0.998	*1.00*	-0.188	0.192	0.330	*0.83*	0.147	0.230	0.523	*1.16*	-0.013	0.124	0.918	*0.99*
Black†	-0.440	0.308	0.155	*0.64*	-0.166	0.316	0.601	*0.85*	-0.485	0.298	0.105	*0.62*	-0.759	0.357	**0.035**	***0.47***	-0.374	0.189	**0.050**	***0.69***
Asian†	-0.569	0.409	0.166	*0.57*	-0.196	0.421	0.643	*0.82*	-0.375	0.404	0.355	*0.69*	0.067	0.464	0.885	*1.07*	-0.321	0.254	0.209	*0.73*

Supplementary Table 9. Linear mixed model-maximum likelihood method. *Natural Log-transformed progression rates. Missing were imputed using mean values. †Proportion. Values in bold indicate statistical significance. *Abbreviations: scFPR: stage-constant annual fibrosis progression rate (assuming constant progression over F0 to F4); β: coefficient; SE: standard error; HCV: hepatitis C virus; HIV: human immunodeficiency virus; RNA: ribonucleic acid; CHC: chronic hepatitis*.

Supplementary Materials

Database search strategy and search strings

1. MEDLINE

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present
Search date: Jan 02, 2018
Limits: 2007 -Current
Filters: BMJ Clinical Evidence - MEDLINE cohort and case-control filter [undated] [Ovid] from website http://www.york.ac.uk/inst/crd/intertasc/observational.htm

Search Strategy:

#	Searches
1	exp cohort studies/
2	cohort$.tw.
3	controlled clinical trial.pt.
4	epidemiologic methods/
5	limit 4 to yr=1966-1989
6	exp case-control studies/
7	(case$ and control$).tw.
8	or/1-3,5-7
9	exp hepatitis C/
10	Hepacivirus/
11	(("parenterally transmitted " or parenterally-transmitted) adj3 ("non a non b hepatitis" or "hepatitis viral non-a non-b")).ti,ab.
12	("hepatitis c" adj2 chronic).ti,ab.
13	(("hepatitis C" or "hepatitis c" or "hepatitis c-like" or "hepatitis c like") adj3 virus$).ti,ab.
14	(virus$ or hepacivirus$ or HCV or "hepatitis c" or "pt-nanbh").ti,ab.
15	or/9-14
16	exp disease progression/
17	((progression? or exacerbation) adj2 disease).ti,ab.
18	fibrosis/
19	Liver Cirrhosis/
20	(fibros$ or cirrhosis).ti,ab.
21	((fibros$ or cirrhosis) adj2 (liver or hepatic)).ti,ab.
22	or/16-21
23	Prognosis/
24	prognos$.ti,ab.
25	disease-free survival/
26	(survival? adj3 ("disease-free" or "disease freeor progression-free" or "progression free" or "event-free" or "event free")).ti,ab.
27	medical futility/
28	(futil$ adj2 (treatment? or medical)).ti,ab.
29	treatment outcome/
30	(treatment adj2 (efficacy or effectiveness or outcome)).ti,ab.
31	(outcome adj2 rehabilitation).ti,ab.
32	treatment failure/
33	(treatment adj2 failure?).ti,ab.
34	morbidity/
35	morbidit$.ti,ab.
36	mortality/
37	(mortalit$ or death rate?).ti,ab.
38	(mortalit$ adj3 (decline? or determinant? or differential or excess)).ti,ab.
39	("death rate?" adj3 ("age-specific" or "age specific")).ti,ab.
40	((death or "case fatality") adj2 rate?).ti,ab.
41	fatal outcome/
42	(outcome? adj2 fatal).ti,ab.
43	hospital mortality/
44	(mortalit$ adj3 (hospital or "in-hospital" or inhospital or "in hospital" or "in-house" or "in house")).ti,ab.

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45	survival rate/
46	(rate adj3 survival adj3 (mean or rate or cumulative)).ti,ab.
47	(survivorship or (survival adj2 (rates or "times mean"))).ti,ab.
48	or/23-47
49	8 and 15 and 22 and 48

2. EMBASE

Databases searched: Embase Classic+Embase 1947 to 2017 December 29
Search date: January 02, 2018
Limits: 2007-Current
Filters: BMJ Clinical Evidence - EMBASE cohort and case-control filter [undated] [Ovid] from website http://www.york.ac.uk/inst/crd/intertasc/observational.htm

Search Strategy:

#	Searches
1	exp hepatitis C/
2	exp hepatitis C virus/
3	(("parenterally transmitted " or parenterally-transmitted) adj3 ("non a non b hepatitis" or "hepatitis viral non-a non-b")).ti,ab.
4	("hepatitis c" adj2 chronic).ti,ab.
5	(("hepatitis C" or "hepatitis c" or "hepatitis c-like" or "hepatitis c like") adj3 virus$).ti,ab.
6	(hepacivirus$ or HCV or "hepatitis c" or "pt-nanbh").ti,ab.
7	or/1-6
8	exp disease course/
9	((progression? or exacerbation) adj2 disease).ti,ab.
10	liver fibrosis/
11	fibrosis.ti,ab.
12	liver cirrhosis/
13	(fibros$ or cirrhosis).ti,ab.
14	((fibros$ or cirrhosis) adj2 (liver or hepatic)).ti,ab.
15	or/8-14
16	prognosis/
17	prognos$.mp.
18	disease-free survival/
19	(survival? adj3 ("disease-free" or "disease freeor progression-free" or "progression free" or "event-free" or "event free")).ti,ab.
20	(futil$ adj2 (treatment? or medical)).ti,ab.
21	treatment outcome/
22	(treatment adj2 (efficacy or effectiveness or outcome)).ti,ab.
23	(outcome adj2 rehabilitation).ti,ab.
24	treatment failure/
25	(treatment adj2 failure?).ti,ab.
26	morbidity/
27	morbidit$.ti,ab.
28	mortality/
29	(mortalit$ or death rate?).ti,ab.
30	(mortalit$ adj3 (decline? or determinant? or differential or excess)).ti,ab.
31	(death rate? adj3 ("age-specific" or "age specific")).ti,ab.
32	fatality/
33	(outcome? adj2 fatal).ti,ab.
34	(mortalit$ adj3 (hospital or "in-hospital" or inhospital or "in hospital" or "in-house" or "in house")).ti,ab.
35	survival rate/
36	(rate adj3 survival adj3 (mean or rate or cumulative)).ti,ab.
37	(survivorship or (survival adj2 (rates or "times mean"))).ti,ab.
38	or/16-37
39	exp cohort analysis/
40	exp longitudinal study/
41	exp prospective study/

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42	exp follow up/
43	cohort$.tw.
44	exp case control study/
45	(case$ and control$).tw.
46	or/39-45
47	7 and 15 and 38 and 46

PUBMED

Databases searched: PubMed

Limits: Publication date from 2007/01/01 to 2018/01/02

Filters: BMJ Clinical Evidence - EMBASE cohort and case-control filter [undated] [Ovid translated into PubMed] from website http://www.york.ac.uk/inst/crd/intertasc/observational.htm

Search Strategy:

((cohort studies[mesh]) OR (cohort$[Title]) OR (epidemiologic methods[mesh:noexp]) OR (case-control studies[mesh]) OR ((case$ AND control$) AND Title) OR (limit AND (epidemiologic methods[mesh:noexp]) AND to yr=1966-1989)) **AND** ((hepatitis C[mesh]) OR (Hepacivirus[mesh:noexp]) OR ((("parenterally transmitted"[tiab] OR parenterally-transmitted[tiab]) AND ("non a non b hepatitis"[tiab] OR "hepatitis viral non-a non-b"[tiab]))) OR (("hepatitis c"[tiab] AND chronic[tiab])) OR ((("hepatitis C"[tiab] OR "hepatitis c"[tiab] OR "hepatitis c-like"[tiab] OR "hepatitis c like"[tiab]) AND virus$[tiab])) OR ((virus$[tiab] OR hepacivirus$[tiab] OR HCV[tiab] OR "hepatitis c"[tiab] OR "pt-nanbh"[tiab]))) **AND** ((disease progression[mesh]) OR (((progression*[tiab] OR exacerbation[tiab]) AND disease[tiab])) OR (fibrosis[mesh:noexp]) OR (Liver Cirrhosis[mesh:noexp]) OR ((fibros$[tiab] OR cirrhosis[tiab])) OR (((fibros$[tiab] OR cirrhosis[tiab]) AND (liver[tiab] OR hepatic[tiab])))) **AND** ((Prognosis[mesh:noexp]) OR (prognos$[tiab]) OR (disease-free survival[mesh:noexp]) OR ((survival*[tiab] AND ("disease-free"[tiab] OR "disease free"[tiab] OR "progression-free"[tiab] OR "progression free"[tiab] OR "event-free"[tiab] OR "event free"[tiab])) OR (medical futility[mesh:noexp]) OR ((futil$[tiab] AND (treatment*[tiab] OR medical[tiab])) OR (treatment outcome[mesh:noexp]) OR ((treatment[tiab] AND (efficacy[tiab] OR effectiveness[tiab] OR outcome[tiab])) OR ((outcome[tiab] AND rehabilitation[tiab])) OR (treatment failure[mesh:noexp]) OR ((treatment[tiab] AND failure*[tiab])) OR (morbidity[mesh:noexp]) OR (morbidit$[tiab]) OR (mortality[mesh:noexp]) OR ((mortalit$[tiab] OR death rate*[tiab])) OR ((mortalit$[tiab] AND (decline*[tiab] OR determinant*[tiab] OR differential[tiab] OR excess[tiab])) OR (("death rate*"[tiab] AND ("age-specific"[tiab] OR "age specific"[tiab])) OR (((death[tiab] OR "case fatality"[tiab]) AND rate*[tiab])) OR (fatal outcome[mesh:noexp]) OR ((outcome*[tiab] AND fatal[tiab])) OR (hospital mortality[mesh:noexp]) OR ((mortalit$[tiab] AND (hospital[tiab] OR "in-hospital"[tiab] OR inhospital[tiab] OR "in hospital"[tiab] OR "in-house"[tiab] OR "in house"[tiab])) OR (survival rate[mesh:noexp]) OR ((rate[tiab] AND survival[tiab] AND (mean[tiab] OR rate[tiab] OR cumulative[tiab])) OR ((survivORship[tiab] OR (survival[tiab] AND (rates[tiab] OR "times mean"[tiab])))))

Supplementary Materials

List of extracted data items

Previously identified data items were abstracted in duplicate by two independent reviewers using piloted abstraction sheets in excel. Study authors were not contacted to obtain missing data. For non-English studies, native speakers were contacted for help with full-text review and data extraction process. Abstract were not included in the current analysis as these records do not report information necessary for estimating prognosis (i.e. duration of infection).

1. **Study related factors:**
   - Study design (i.e. cross-sectional/retrospective, retrospective-prospective, prospective)
   - Study setting (i.e. clinical, non-clinical)
   - Study population (i.e. blood donor, female cohort, dialysis patient, IDUs, community, pediatric, post-transfusion, renal transplant recipients)
   - Sample size
   - Country
2. **Host-related factors:**
   - Gender (n, % male)
   - Mean age at assessment of liver disease (years)
   - Mean age at HCV acquisition [where unavailable, data were calculated by taking the difference between mean age at assessment of liver disease and the mean duration of HCV infection] (years)
   - Mean estimated duration of HCV infection (years)
   - Mode of HCV acquisition (n, %: IDU, blood transfusion, sporadic)
   - Excess alcohol consumption [as defined in study] (n, %)
   - Mean body mass index (BMI) (kg/m^2)
   - History of diabetes mellitus (n, %)
   - Coinfection with HBV (n, % HBsAg positive)
   - Coinfection with HIV (n, %)
3. **Virus related factors:**
   - HCV genotype (n, %: G1, G2, G3, G4, other)
   - HCV RNA positivity (n, %)
   - HCV RNA viral load (IU/ml)
4. **Liver-related factors**
   - Elevated ALT levels (n, %)
   - Mean ALT (IU/L)
   - Presence of hepatic steatosis (n, %)
   - Method of fibrosis assessment (e.g. LB, TE, combination LB and non-invasive)
   - Method of fibrosis scoring (e.g. METAIR, Ishak, or cutoffs for non-invasive tests)
   - Fibrosis stage distributions at latest available follow-up point (n, %: F0 to F4) [where data were reported as composite (i.e., F0/F1) a 50:50 distributions was applied to the 2 stages. Stage distribution was not performed if more than two stages were reported in composite]
   - Liver biopsy length (mm)
   - Clinical or histological diagnosis of cirrhosis (n. %)
   - Mean histological activity index (HAI) Inflammatory score

Note on missing data: Age at infection, for studies that did not report this, was imputed by taking the difference between age at assessment and the duration of infection. For studies that report composite fibrosis stages (e.g., F0/F1), data were distributed 50:50 across F0 and F1. Stage distribution was not performed when more than two stages were reported collectively (e.g., F0/F1/F2).

Supplementary Materials

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MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	5-6
2	Hypothesis statement	6; [Objectives-Descriptive study]
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6 [Natural history of CHC (treatment-naïve)]
5	Type of study designs used	6
6	Study population	6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	6-7
8	Search strategy, including time period included in the synthesis and key words	6-7, [56-58; Supplemental methods]
9	Effort to include all available studies, including contact with authors	6-7, [56-58; Supplemental methods]
10	Databases and registries searched	6-7, [55-58; Supplemental methods]
11	Search software used, name and version, including special features used (eg, explosion)	6-7, [56-58; Supplemental methods]
12	Use of hand searching (eg, reference lists of obtained articles)	6-7
13	List of citations located and those excluded, including justification	[Figure 1] [29-31; Supplemental methods]
14	Method of addressing articles published in languages other than English	7, [59; Supplemental methods]
15	Method of handling abstracts and unpublished studies	7, [59; Supplemental methods]
16	Description of any contact with authors	7,[59; Supplemental methods]
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-8; [Table1]
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7,27,54 [TableS1]
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	7,27,54 [TableS1]
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	8-9
21	Assessment of study quality, including blinding of quality assessors, stratification or	8-9

	regression on possible predictors of study results	
22	Assessment of heterogeneity	9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8-9
24	Provision of appropriate tables and graphics	[Fig1]; [Figure S2-S5; Supplemental Methods]
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	[FigS1; FigS2-FigS5; Supplemental Methods]
26	Table giving descriptive information for each study included	[TableS3, TableS4; Supplemental Methods]
27	Results of sensitivity testing (eg, subgroup analysis)	11-13; [Table2], [Fig2], [TableS7]
28	Indication of statistical uncertainty of findings	12-13; [Table2], [Table 3]

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	14-15
30	Justification for exclusion (eg, exclusion of non-English language citations)	16
31	Assessment of quality of included studies	16
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	14
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	14-15
34	Guidelines for future research	15-16
35	Disclosure of funding source	1

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.