Supplementary Materials

List of Supplementary Materials:

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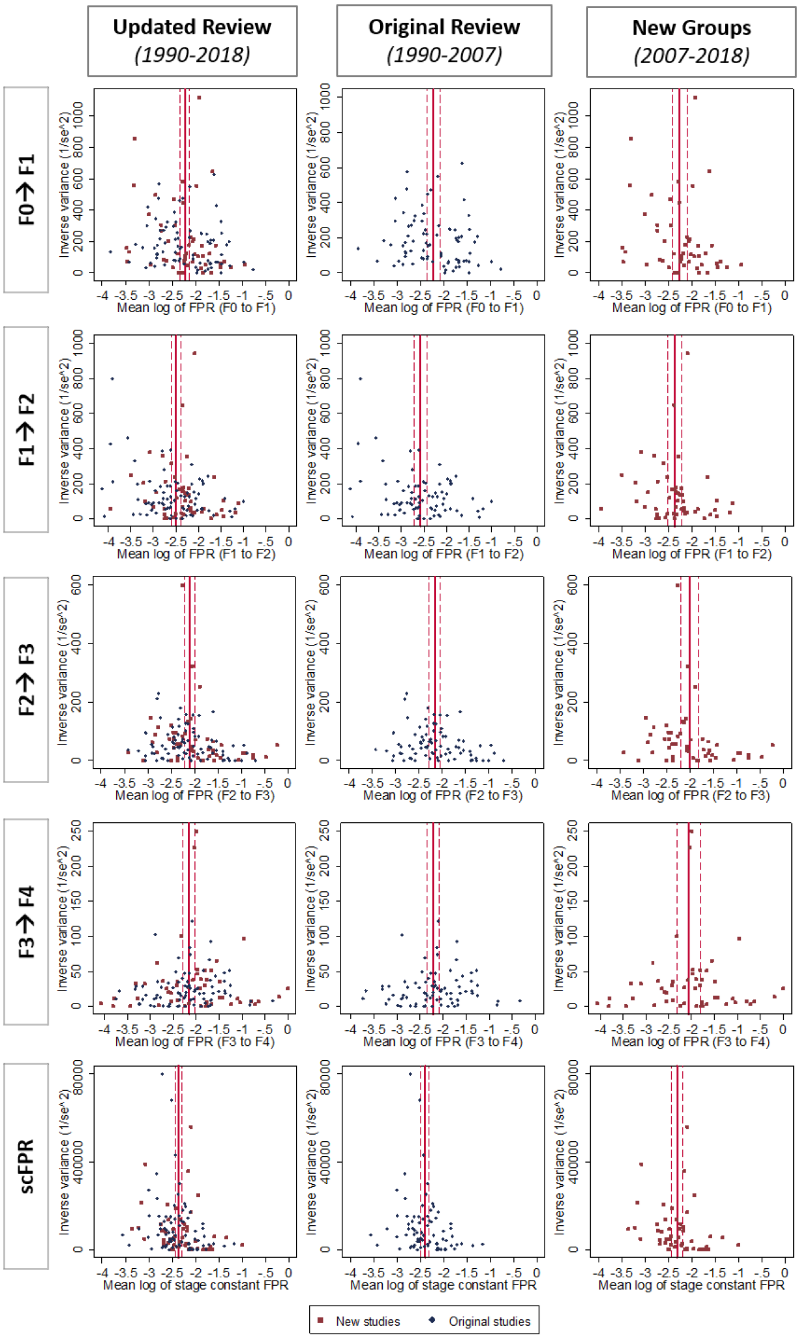
S1 Figure: Funnel plots for hepatic fibrosis progression rate



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.

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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.

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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

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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 (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.

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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 more severe histological liver injury than hemodialysis patients? Am J Nephrol. 2007;27(2):191-196. doi:10.1159/000100892.

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.

42. Besheer T, El-Bendary M, Elalfy H, et al. Prediction of Fibrosis Progression Rate in Patients with Chronic Hepatitis C Genotype 4: Role of Cirrhosis Risk Score and Host Factors. J Interf Cytokine Res. 2017;37(3):97-102. doi:10.1089/jir.2016.0111.

43. Midgard H, Hajarizadeh B, Cunningham EB, et al. International Journal of Drug Policy Changes in risk behaviours during and following treatment for hepatitis C virus infection among people who inject drugs : The ACTIVATE study. 2017;47:230-238. doi:10.1016/j.drugpo.2017.05.040.

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.

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

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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

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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

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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

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Supplementary Table 7 continued

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

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Supplementary Table 7 continued

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 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). Additional data form the original study (2008) by Thein et al is available though:* https://aasldpubs.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fhep.22375&file=hep22375-SupplementaryAppendices.doc

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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: . BT: . SP: .	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: 24.9 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 – 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/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	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/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

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)
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 Materials

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. 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. Additional data form the original study (2008) by Thein et al is available though:* https://aasldpubs.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fhep.22375&file=hep22375-SupplementaryAppendices.doc

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

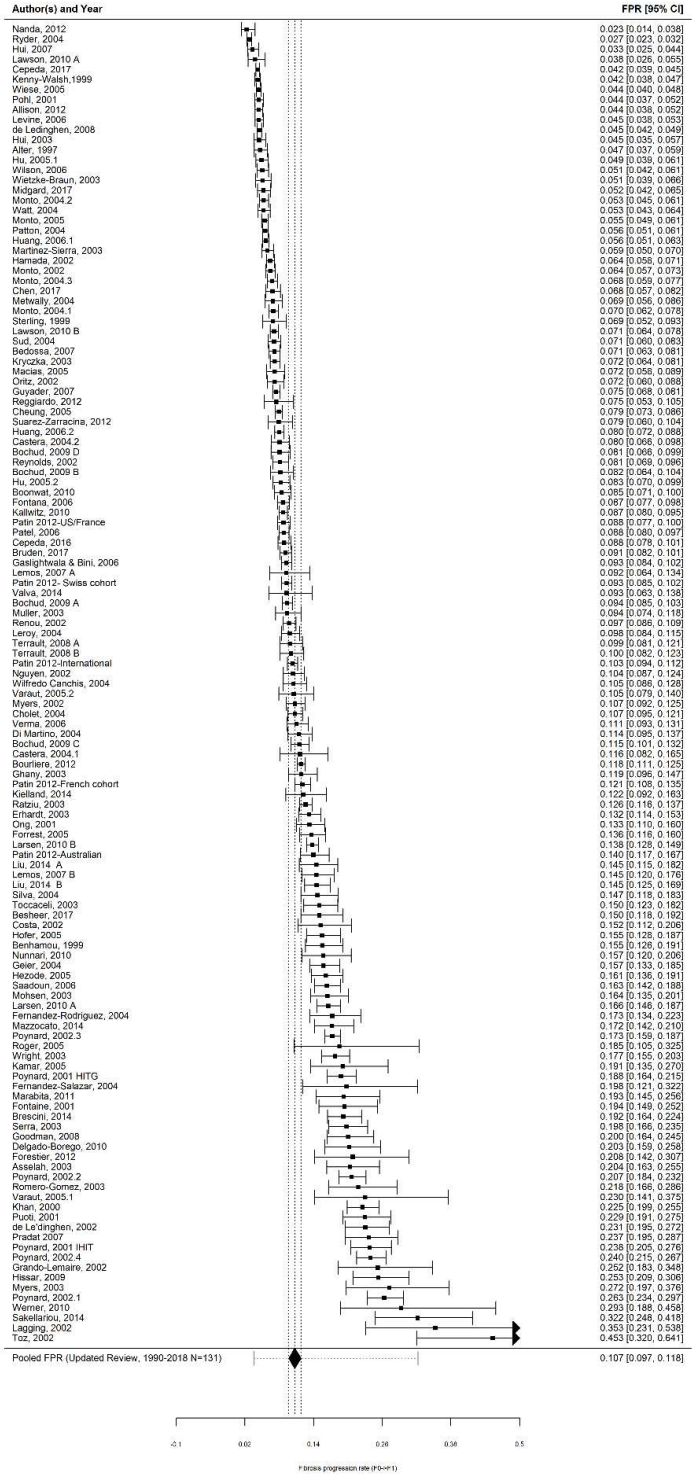
S7 Table: Hepatic fibrosis progression rates stratified by review update

	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.*

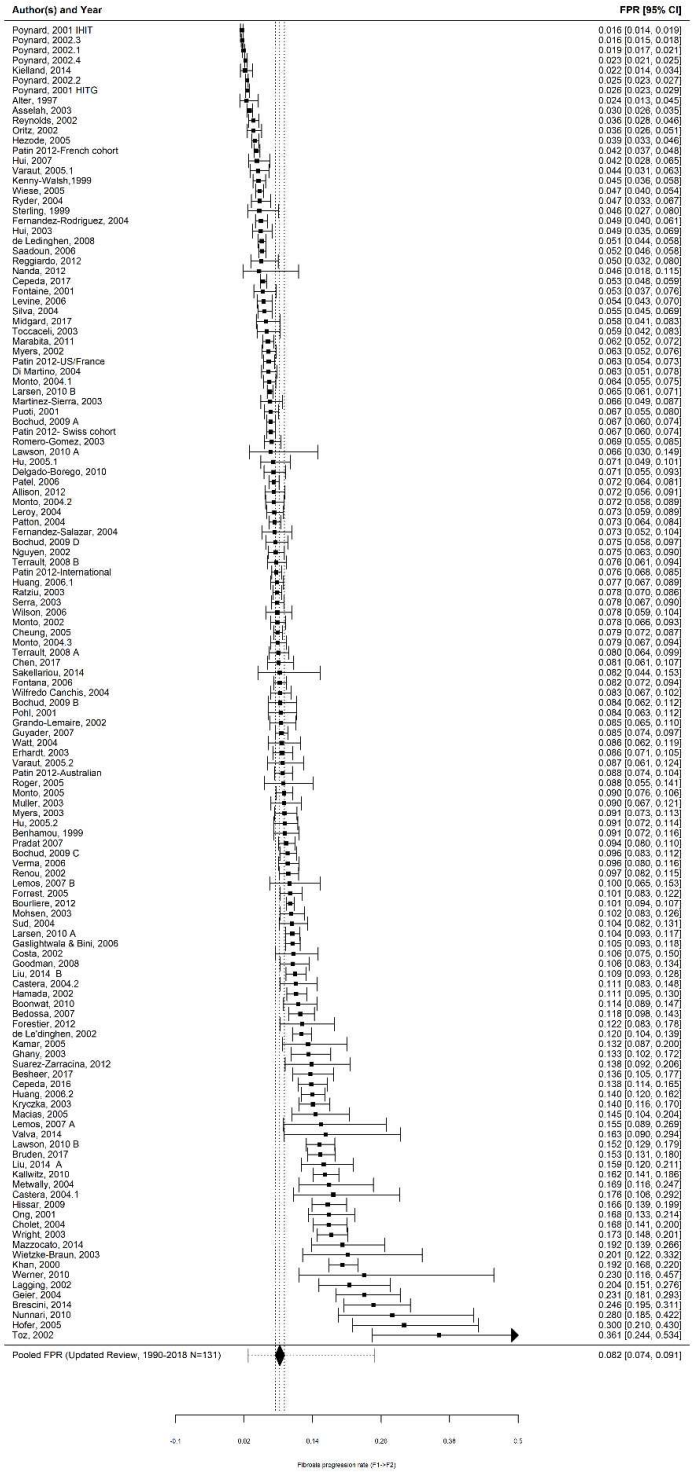
Supplementary Materials

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



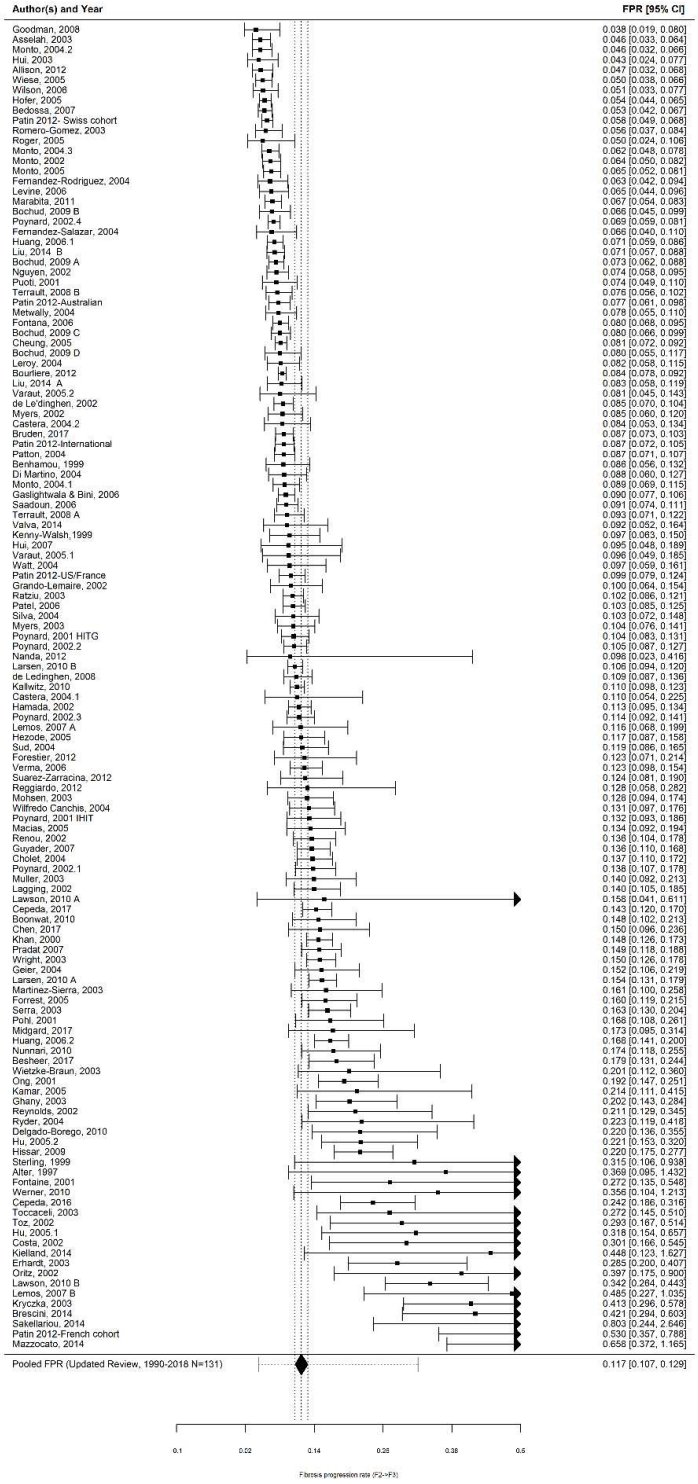
Supplementary Materials

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



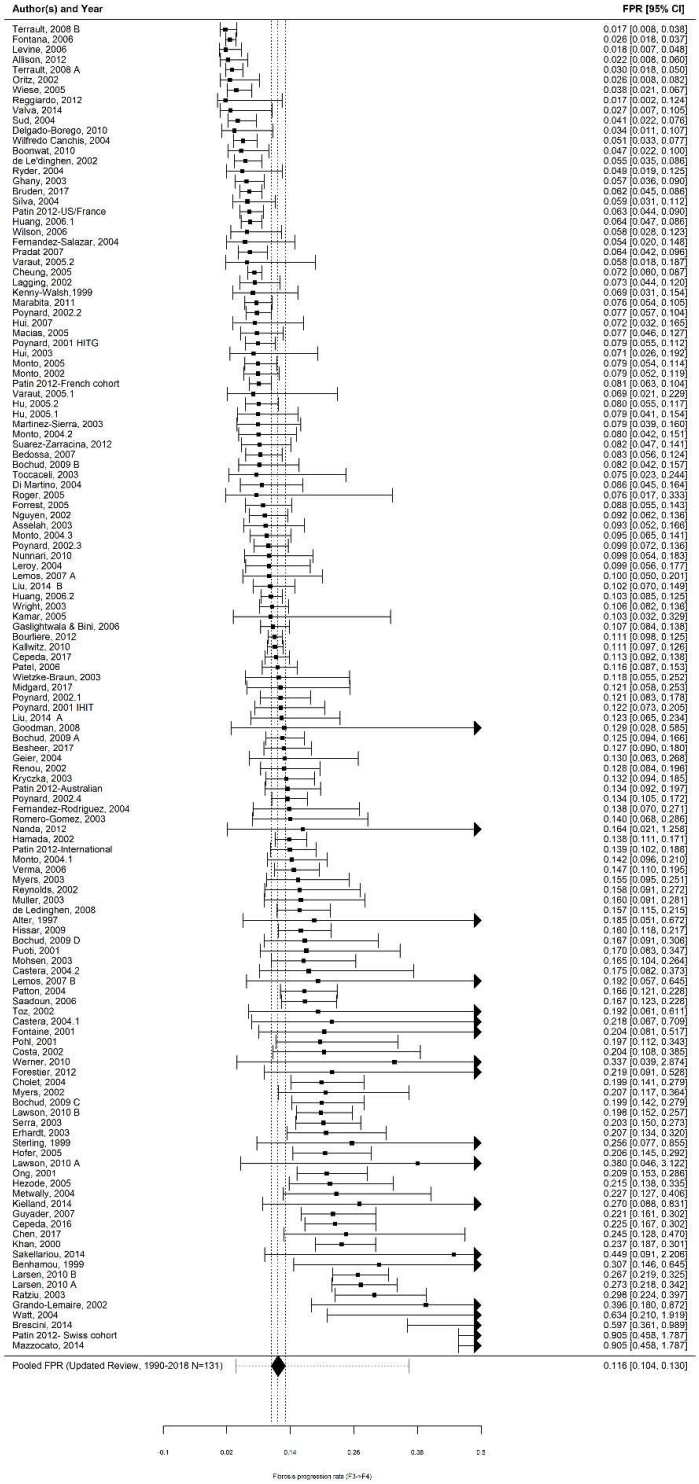
Supplementary Materials

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*
	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 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

Predictors	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
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.

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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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