

Estimation of Stage-Specific Fibrosis Progression Rates in Chronic Hepatitis C Virus Infection: A Meta-Analysis and Meta-Regression

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Published estimates of liver fibrosis progression in individuals with chronic hepatitis C virus (HCV) infection are heterogeneous. We aimed to estimate stage-specific fibrosis progression rates and their determinants in these individuals. A systematic review of published prognostic studies was undertaken. Study inclusion criteria were as follows: (1) presence of HCV infection determined by serological assays; (2) available information about age at assessment of liver disease or HCV acquisition; (3) duration of HCV infection; and (4) histological and/or clinical diagnosis of cirrhosis. Annual stage-specific transition probabilities ($F0 \rightarrow F1$, . . . , $F3 \rightarrow F4$) were derived using the Markov maximum likelihood estimation method and a meta-analysis was performed. The impact of potential covariates was evaluated using meta-regression. A total of 111 studies of individuals with chronic HCV infection ($n = 33,121$) were included. Based on the random effects model, the estimated annual mean (95% confidence interval) stage-specific transition probabilities were: $F0 \rightarrow F1$ 0.117 (0.104-0.130); $F1 \rightarrow F2$ 0.085 (0.075-0.096); $F2 \rightarrow F3$ 0.120 (0.109-0.133); and $F3 \rightarrow F4$ 0.116 (0.104-0.129). The estimated prevalence of cirrhosis at 20 years after the infection was 16% (14%-19%) for all studies, 18% (15%-21%) for cross-sectional/retrospective studies, 7% (4%-14%) for retrospective-prospective studies, 18% (16%-21%) for studies conducted in clinical settings, and 7% (4%-12%) for studies conducted in nonclinical settings. Duration of infection was the most consistent factor significantly associated with progression of fibrosis. **Conclusion:** Our large systematic review provides increased precision in estimating fibrosis progression in chronic HCV infection and supports nonlinear disease progression. Estimates of progression to cirrhosis from studies conducted in clinical settings were lower than previous estimates. (HEPATOLOGY 2008;48:418-431.)

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injecting/intravenous drug use(r); MMLE, Markov maximum-likelihood estimation.

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Hepatitis C virus (HCV) is the most common cause of end-stage liver disease and the leading indication for liver transplantation.¹ Although chronic HCV infection can progress slowly to liver fibrosis and the subsequent development of cirrhosis, liver failure, and hepatocellular carcinoma, progression can also be rapid. Some published reports suggest that the prognosis of HCV is benign, with only 2%-3% developing cirrhosis at 20 years after infection.²⁻⁴ Other reports suggest that the prognosis is much worse, with 51% of patients developing cirrhosis at 22 years.⁵ Consequently, the true prognosis of HCV infection is still beset by controversy. Previous studies have explored the effect of study design, setting, study population, and methods used to estimate fibrosis progression as potential sources of variability among published estimates of prognosis.⁶⁻⁸ A previous systematic review and meta-analysis by Freeman et al.⁶ have shown varying progression rates among different populations. In their review, higher rates of progression to cirrhosis were reported for posttransfusion cohorts and cross-sectional liver clinic series, and much lower rates for

blood donors and community cohorts. These results suggest that selection biases and differences in the prevalence of factors associated with more rapid disease progression across study types, such as older age at HCV infection, male gender, and excess alcohol intake, might explain variability in progression rates.^{5,6,9-11}

The method of estimating fibrosis progression rates between liver fibrosis stages (commonly expressed using the METAVIR scoring system, F0 to F4)¹² may also affect prognosis. Two approaches have been used to estimate fibrosis progression rates: an indirect method, using a single biopsy and the estimated date of HCV infection; and a direct method, using serial liver biopsies and the interval between two adjacent biopsies.⁸ Most previous estimates^{6,8,13,14} have been based on the indirect method and have consequently assumed that progression rates are constant across fibrosis stages. However, some evidence suggests that fibrosis may accelerate with time and that rates of progression may vary between stages^{15,16} and between-patient and within-patient populations.^{8,17-21} Although the direct method has the ability to calculate stage-specific transition rates, very few studies include patients with more than a single biopsy. Yi et al.¹⁵ have recently described an indirect method (Markov maximum likelihood estimation, MMLE) that allows more accurate estimation of stage-specific transition probabilities. This involves representation of HCV prognosis as a series of fibrosis stages in a Markov model, and the estimation of the most likely transition probability for each stage transition (for example, F0→F1) for each study. This method does not require the assumption that the rate of transition between each fibrosis stage is constant. In fact, application of this method has supported the hypothesis that rates of fibrosis vary between stages, and suggested that methods that assume constant stage transition probabilities may lead to substantial inaccuracy in very long-term projections of HCV prognosis.¹⁵

More accurate estimates of liver fibrosis progression are required in order to reliably predict the current and future burden of disease for the whole HCV-infected population, a highly heterogeneous group of patients, as well as to perform cost-effectiveness analyses of antiviral therapies in selective groups or settings. The objectives of our systematic review and meta-analysis were to improve the precision of fibrosis progression rates by estimating stage-specific transition probabilities from up to date published studies of HCV natural history using the MMLE method and to investigate the effect of covariates including study design, population, setting, and clinical factors on these rates.

Patients and Methods

Search Strategy and Selection Criteria

Published human studies that examined liver fibrosis progression in chronic HCV infection were searched via the MEDLINE, EMBASE, and PubMed databases of both English and non-English language publications, covering the period January, 1990 to August, 2007 (up to December, 2006 for non-English articles), with combinations of “hepatitis C,” “HCV,” “hepatitis non-A,” “fibrosis,” “cirrhosis,” “cohort studies,” “case-control studies,” “prognosis,” “disease-free survival,” “medical: futile,” “treatment outcome,” “treatment failure,” “disease progression,” “morbidity,” “mortality,” “fatal outcome,” “hospital mortality,” “survival analysis,” and “natural history.” Citations were cross-checked through review of bibliographies of relevant published papers. Additionally, an expert working in the area was contacted to supplement any gray literature (see Fig. 1).

Studies were included if they satisfied the following criteria: (1) full-length and peer-reviewed original articles; (2) chronic HCV infection 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 positivity, an elevated alanine aminotransferase (ALT) level without an alternative cause of chronic liver disease, liver biopsy consistent with chronic hepatitis C; and (3) no HCV treatment prior to the first liver biopsy or between subsequent biopsies. Studies were excluded if there were reports of fewer than 20 cases of chronic HCV infection, or if fibrosis progression rates could not be calculated (for example, duration of HCV infection not reported). If duplicate publications represent several updates of the data, the most recent data or studies with more complete information were included.

Data Abstraction

Data were collected for each study using data abstraction forms that included relevant items identified in previous studies: (1) study-related factors; (2) host-related factors—age at assessment, gender, body mass index, age at HCV infection, estimated duration of HCV infection, mode of HCV acquisition, alcohol consumption, human immunodeficiency virus (HIV) or hepatitis B virus coinfection, history of diabetes mellitus, and presence of hepatic steatosis; (3) virus-related factors—HCV genotype, HCV RNA positivity, and HCV viral load; and (4) liver-related factors—ALT level, fibrosis stage based on established histopathologic criteria,^{12,22-24} clinical and/or histological diagnosis of cirrhosis, and histological activity index. We accepted the definitions of elevated ALT level

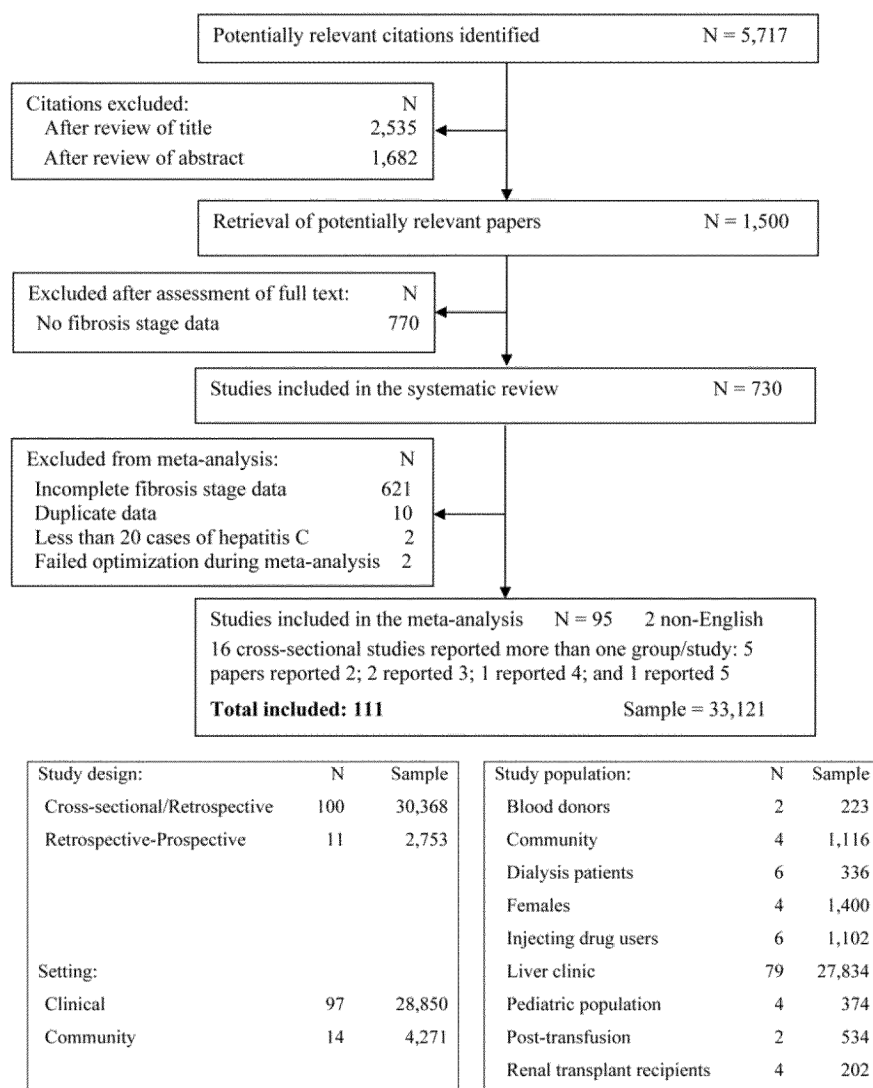


Fig. 1. Identification of relevant literature of the natural history of hepatitis C.

and excess alcohol consumption reported in the studies. We collected the past history of alcohol consumption when possible.

The mean age at HCV acquisition was calculated by taking the difference between the mean age at assessment of liver disease and the mean duration of HCV infection when direct information about age at infection was not available. Ishak et al.²³ fibrosis stages (S0-S6) were converted to the well-validated METAVIR scoring system,¹² in which stage of fibrosis is assessed on a five-point scale: F0 no fibrosis, F1 portal fibrosis without septa, F2 portal fibrosis with rare septa, F3 numerous septa without cirrhosis, F4 cirrhosis (that is, S0 F0; S1 F1; S2 F2; S3-S4 F3; S5-S6 F4). When studies (n = 16) reported two immediately adjacent fibrosis stages collectively, for example, F0/F1 or F3/F4, a 50:50 distribution was made conservatively for each stage (for example, 20 cases of F0 or F1 were distributed to 10 F0 and 10 F1).

For the Knodell scoring system (F0 to F4 without F2 stage), F3 was similarly distributed to F2 and F3. Stage distribution was not performed if three or more stages were reported collectively.

Statistical Analysis

Eligible studies were mainly grouped by study design, setting and population: (1) study design — cross-sectional/retrospective, retrospective-pro prospective, and prospective; (2) setting — clinical and nonclinical; (3) study population — blood donors, community, patients on dialysis, female cohorts, injecting/intravenous drug users (IDUs), liver clinic series, pediatric population, posttransfusion cohorts, and renal transplant recipients (described further in Table 1).

Estimation of Fibrosis Progression Rates. We used two methods to estimate fibrosis progression rates: (1) the MMLE method developed and validated by Yi et al.¹⁵ to

Table 1. Description of Studies of Individuals with Chronic Hepatitis C Virus Infection

	Description
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. ⁴²
Retrospective-prospective	Retrospective-prospective studies 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; ^{2-4,42-44} Asymptomatic blood donors found to be repeatedly anti-HCV (antibody to hepatitis C virus)-positive on routine screening underwent interviews for potential risk factors and laboratory testing for evidence of liver disease and serological markers of hepatitis A and B. ^{29,45-47} One blood donor series, three female cohorts, one injecting drug users, three liver clinic series, two pediatric population, and one posttransfusion cohort were included in the analysis.
Prospective	Prospective studies begin with the onset of the infection, probable infection can be inferred, for example, identified cases of acute transfusion-associated non-A, non-B, or type C hepatitis, and are prospectively followed. ^{34,38,39,42,48} There is no prospective study included in the analysis.
Study setting	
Clinical	Individuals were identified and/or assessed for their HCV status and liver disease in a clinical/tertiary care setting.
Nonclinical	Individuals were screened for HCV in a nonclinical setting, for example, blood donation center or regional center.
Study population	
Blood donors	Individuals newly diagnosed with chronic HCV infection at blood donor screening. ^{29,46}
Community	HCV-infected individuals identified or participating in national health screening or studies conducted in nonclinical settings. ^{31,49-51}
Dialysis patients	HCV-infected individuals with end-stage renal disease receiving dialysis and awaiting renal transplantation. ⁵²⁻⁵⁷
Female cohorts	A population of otherwise healthy females infected with HCV after exposure to contaminated anti-D immunoglobulin, where the date of infection was known were identified through national screening programs or documentation at the maternity clinics and subsequently examined in regional clinics of infectious diseases; ^{2-4,43,44,58} A single study by Di Martino et al. ⁵⁹ examined the effect of estrogen on liver fibrosis progression in HCV-infected females.
Injecting drug users	Individuals who acknowledged injection drug use as the main risk factor for HCV infection. ^{60-64,65}
Liver clinic	HCV-infected individuals referred to specialist liver clinics for further assessment.
Pediatric population	Survivors of childhood cancer, who were at risk of contracting HCV from receipt of blood products prior to the initiation of HCV blood donor screening; HCV identified through a transfusion look-back program; asymptomatic HCV-infected children who underwent liver biopsies for diagnostic purposes or as part of a screening protocol for HCV treatment. ^{30,33,66,67}
Posttransfusion cohorts	Individuals with posttransfusion non-A, non-B hepatitis defined by persisting ALT elevations following transfusion, in the absence of an alternative cause, subsequently found to have chronic HCV infection when diagnostic anti-HCV testing became available, and a documented date of blood transfusion; ⁶⁸ individuals with congenital bleeding abnormalities and abnormal liver biochemistry. ⁶⁹
Renal transplant recipients	Individuals who had functioning graft; the exact date of HCV infection was determined using historical frozen sera or assumed to be the date of the first dialysis or first blood transfusion. ^{56,57,70,71}
Presumed date of HCV infection	Date of transfusion of blood or blood products prior to 1992, when serologic screening of donated blood for HCV became widely available, the first year of injecting drug use, or the date of a single specific and convincing parenteral exposure (for example, needle-stick injury).
Estimated duration of HCV infection	Defined as the time elapsed from the presumed date of infection to the date of liver biopsy. ⁸ 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.
Liver fibrosis staging	
Batts and Ludwig ⁷²	F0 normal connective tissue; F1 fibrous portal expansion; F2 periportal or rare P-P septa; F3 fibrous septa with architectural distortion, but no obvious cirrhosis; and F4 cirrhosis.
Conventional method	Histological classification reported as chronic persistent hepatitis, chronic active hepatitis, and cirrhosis.
Desmet et al. ²²	F0 no fibrosis; F1 mild fibrosis; F2 moderate fibrosis; F3 severe fibrosis; and F4 cirrhosis.
Ishak et al. ²³	Stage 0 no fibrosis; Stage 1 fibrous expansion of some portal areas, with or without short fibrous septa; Stage 2 fibrous expansion of most portal areas, with or without short fibrous septa; Stage 3 fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging; Stage 4 fibrous expansion of portal areas with marked bridging (portal to portal (P-P) as well as portal to central (P-C); Stage 5 marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis); and Stage 6 cirrhosis, probable or definite.
Knodell et al. ⁷³	F0 no fibrosis; F1 fibrous portal expansion; F3 bridging fibrosis (P-P or P-C linkage); and F4 cirrhosis.
Ludwig ⁷⁴	F1 no fibrosis or fibrosis confined to enlarged portal tracts; F2 periportal fibrosis or P-P septa but intact architecture; F3 septal fibrosis with architectural distortion, but no obvious cirrhosis; and F4 probable or definite cirrhosis.
Bedossa and Poynard ¹² (METAVIR)	F0 no fibrosis; F1 portal fibrosis without septa; F2 portal fibrosis with rare septa; F3 numerous septa without cirrhosis; F4 cirrhosis.
Scheuer ²⁴	F0 none; F1 enlarged, fibrotic portal tracts; F2 periportal or portal-portal septa, but intact architecture; F3 fibrosis with architectural distortion, but no obvious cirrhosis; and F4 probable or definite cirrhosis.
Wong et al. ⁷⁵	Stage 0 none; Stage 1 confined to portal tracts; Stage 2 portal tracts plus spurs radiating into parenchyma; Stage 3 linkage of some portal tracts but intact architecture; Stage 4 linkage of most portal tracts with architectural distortion; and Stage 5 cirrhosis.

Abbreviations: CV, hepatitis C virus; ALT, alanine aminotransferase.

estimate annual stage-specific transition probabilities (for example, $F0 \rightarrow F1$, . . . , $F3 \rightarrow F4$); and (2) the indirect (stage-constant) method that assumes that fibrosis progression rates are constant. Our estimation of stage-specific transition probabilities were based on reported prevalence of liver fibrosis stages (F0-F4) and duration of HCV infection. Assessment of liver fibrosis stage was generally by histopathologic examination of liver tissue at the latest follow-up point in longitudinal studies, if available, and at time of recruitment in cross-sectional/retrospective studies. Although different fibrosis staging systems were employed, cirrhosis was defined on the basis of well-established histopathologic criteria.¹² In those studies that also used nonhistopathologic criteria, these were based on clinical, laboratory, and ultrasound evidence consistent with cirrhosis.²⁵

In the stage-constant method,⁸ the METAVIR stage was divided by the estimated number of years of infection (person-years). Person-years were calculated by multiplying the mean duration of infection by the meta-analysis sample size. For example, in a study reporting a stage distribution of 10 F0, 20 F1, 15 F2, 5 F3, and 5 F4 with an estimated mean duration of infection of 15 years, the mean fibrosis progression rate is calculated as follows: $[(10 \ 0) \ (20 \ 1) \ (15 \ 2) \ (5 \ 3) \ (5 \ 4)] / [(10 \ 20 \ 15 \ 5 \ 5) \ 15] = 0.103$ fibrosis units per year.

Meta-Analysis and Meta-Regression. A meta-analysis was performed to estimate pooled transition probabilities derived using both the MMLE method and the stage-constant method. Both fixed and random effects model estimates were obtained. The effect of individual studies on the pooled stage-specific transition probabilities was assessed by re-estimating the overall effect after omitting each study. We examined study-specific data graphically through the production of funnel plots for apparent heterogeneity across studies and potential publication bias, and tested for significance with Egger's test for asymmetry.²⁶ Next, the cumulative probability of cirrhosis (mean and 95% confidence intervals [CIs]) up to 30 years after HCV exposure was estimated, using the estimated progression rates and their lower and upper bounds.

The impact of potentially important covariates on fibrosis progression was examined by a univariate regression analysis and a random effects model meta-regression to explore sources of heterogeneity both within-studies and between-studies. For the meta-regression, we used a linear mixed model—maximum likelihood method, adjusting for covariates. We first imputed values for missing data by using the mean value of the studies without missing data.

The meta-regression model included study design and population as described above, publication year (before the year 2000, and in the year 2000 and after), proportion of males, age at HCV infection, duration of infection, proportion of IDU, blood or blood product transfusion, excess alcohol consumption, HIV positivity, HCV RNA positivity, and genotype as explanatory factors, and natural log of stage-specific transition probabilities as dependent variables. The regression was weighted by the use of a multiplicative variance adjustment factor, taking into account both within-study variances of transition probabilities and the residual between-study heterogeneity.²⁷ A two-sided significance level of 0.05 was used in all statistical procedures. Statistical analysis was performed with SAS version 9.1 and the PROC MIXED ML procedure²⁸ was employed for meta-regression.

Results

Study Characteristics. A total of 111 reports of HCV natural history studies, involving 33,121 individuals with chronic HCV infection were included in the meta-analysis (Fig. 1). A total of 100 of 111 studies had a cross-sectional/retrospective design (Table 2). Most studies ($n = 97$) were performed in clinical settings. Only 14 studies were performed in nonclinical settings. The population studied was most frequently liver clinic patients ($n = 79$; Table 3). Supplementary Appendices A through C report the study and clinical characteristics of study subjects in the 111 individual reports.

Table 2 reports summary data characterizing studies stratified by study design and setting. Cross-sectional/retrospective studies differ from retrospective-prospective studies in the proportion of males (64% versus 44%), individuals reporting IDU as a risk factor for HCV infection (43% versus 22%), steatosis (47% versus 19%), and genotype 1 (51% versus 74%). Clinical setting-based studies differ from nonclinical setting-based studies in the proportion of males (64% versus 49%), individuals reporting receipt of blood or blood product as a risk of HCV infection (33% versus 18%), and genotype 1 (52% versus 64%).

Table 3 reports clinical characteristics of study participants stratified by the population of the study. The estimated duration of HCV infection was shorter in the dialysis patients (13 years) and renal transplant recipients (11 years) compared to other populations (16-28 years). Genotype 1 was more prevalent in the female cohorts (91%), renal transplant recipients (67%), and community (63%) than other populations (approximately 50% or less).

Table 2. Summary of Clinical Characteristics of Individuals with Chronic Hepatitis C Virus Infection for All Studies and by Study Design and Setting

Variable	Study Design						Setting			
	All Studies		Cross-Sectional/ Retrospective		Retrospective- Prospective		Clinical-Based		Nonclinical-Based	
	N Studies	Mean	N Studies	Mean	N Studies	Mean	N Studies	Mean	N Studies	Mean
Sample size	111	270	100	275	11	217	97	269	14	271
Liver biopsy (%)	111	95	100	96	11	87	97	96	14	87
Age at assessment (years)	111	43.0	100	43.1	11	42.6	97	42.9	14	43.6
Male (%)	111	62	100	64	11	44	97	64	14	49
BMI (kg/m ²)	34	26.2	31	26.2	3	26.2	31	26.2	3	25.9
Age at HCV acquisition (years)*	111	25.5	100	26.0	11	21.0	97	25.8	14	23.7
Duration of HCV infection (years)	111	17.5	100	17.0	11	21.2	97	17.1	14	20.0
Injecting drug use (%)	95	41	84	43	11	22	81	41	14	40
Blood transfusion (%)	95	31	84	30	11	34	81	33	14	18
Sporadic (%)	97	27	86	28	11	19	83	28	14	22
ALT value	39	88.9	32	90.1	7	83.7	35	91	4	67.0
Elevated ALT (%)	53	75	44	79	9	56	44	77	9	66
Alcohol consumption >20 g/day (%)	91	19	82	19	9	12	81	19	10	19
Steatosis (%)	29	44	26	47	3	19	26	42	3	59
HIV (%)	81	2	76	2	5	6	73	1	8	9
HBV (HBsAg positive) (%)	84	0.5	78	0.4	6	1	76	0.4	8	1
HCV RNA positive (%)	98	95	87	95	11	97	85	95	13	97
Log ₁₀ serum HCV RNA copies/mL (IU/mL)	33	6.2	31	6.2	2	5.8	31	6.2	2	6.2
Genotype 1 (%)	89	54	80	51	9	74	77	52	12	64
Genotype non-1 (%)	89	26	80	26	9	17	77	27	12	18
HAI	22	6.4	21	6.3	1	8.7	20	6.5	2	5.7

*Mean age at HCV infection was calculated by taking the difference between the mean age at assessment of liver disease and the mean duration of HCV infection when direct information about age at infection was not available. Abbreviations: HCV, hepatitis C virus; BMI, body mass index; ALT, alanine aminotransferase; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HBsAg, hepatitis B virus surface antigen; RNA, ribonucleic acid; HAI, histological activity index.

For all studies, the majority of subjects were males (62%), and the mean age at HCV infection and estimated duration were 25.5 years and 17.5 years, respectively (Table 2). The proportion of IDU as a risk factor for HCV infection was 41%, blood or blood product transfusion was 31%, and no obvious risk factor (sporadic) was 27%. Excess alcohol consumption was defined in 83 studies: >20 g/day in five; >40 g/day in 25; >50 g/day in 43; and >80 g/day in 10. The proportion of individuals with excess alcohol consumption was 19%, the proportion with HIV positivity was 2%, HCV RNA positivity was 95%, and genotype 1 was 54%. Liver biopsy was performed in 95% of the individuals. Fibrosis stage distribution was 17% F0, 35% F1, 22% F2, 14% F3, and 12% F4. There were a total of 3,366 cases of cirrhosis and 545,839 person-years of follow-up. Six studies^{4,29-33} included clinical diagnosis of cirrhosis and/or hepatocellular carcinoma.

Estimated Transition Probabilities. The pooled estimate of transition probabilities and estimates stratified by study design and setting are reported in Table 4 (individual study estimates are given in Supplementary Appendix D). Estimates for study populations, and age-specific and duration of HCV infection-specific estimates are re-

ported in Table 5. Due to the presence of significant heterogeneity in the stage-specific transition probabilities between most studies, results from the fixed effects model are interpreted with caution. However, estimates derived from the random effects model are not substantially different from those derived from the fixed effects model. Based on the random effects model, the pooled (95% CI) stage-specific transition probabilities per year were as follows: F0→F1 0.117 (0.104-0.130); F1→F2 0.085 (0.075-0.096); F2→F3 0.120 (0.109-0.133); and F3→F4 0.116 (0.104-0.129). The corresponding median (interquartile range) estimates were 0.111 (0.072-0.188), 0.084 (0.063-0.118), 0.118 (0.082-0.192), and 0.116 (0.075-0.195). The adjusted estimates (that is, estimates adjusted for covariates in Table 6) did not appear to be different from the unadjusted pooled estimates.

The mean estimates for retrospective-prospective studies were lower than those of cross-sectional/retrospective studies for all stages (Table 4). Similarly, clinical setting-based studies had lower estimates compared to nonclinical setting-based studies. Estimates for blood donors and female cohorts were lower than other populations for most stages (Table 5). Individuals who were older (>30 years) when HCV infection was acquired had higher es-

Table 3. Summary of Clinical Characteristics of Populations with Chronic Hepatitis C Virus Infection

Variable	Blood Donors		Community		Dialysis Patients		Females		IDUs		Liver Clinic		Pediatric		Post-transfusion		Renal Transplant	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Sample size	2	112	4	279	6	56	4	350	6	184	79	352	4	94	2	267	4	51
Liver biopsy (%)	2	96	4	82	6	100	4	90	6	82	79	98	4	80	2	95	4	85
Age at assessment (years)	2	37.9	4	46.2	6	44.3	4	49.5	6	36.5	79	44.6	4	15.5	2	43.9	4	39.8
Male (%)	2	69	4	50	6	62	4	0	6	77	79	64	4	51	2	67	4	68
BMI (kg/m ²)	0		2	26.7	1	26.3	0		1	24.3	30	26.2	0		0		0	
Age at HCV acquisition (years)*	2	19.5	4	25.9	6	31.5	4	27	6	20.5	79	26.5	4	3.0	2	22.8	4	29.8
Duration of HCV infection (years)	2	18.4	4	20.7	6	12.5	4	21.8	6	16.0	79	18.0	4	11.1	2	27.5	4	10.5
Injecting drug use (%)	2	34	4	43	4	21	4	6	6	89	69	43	4	4	2	0	0	
Blood transfusion (%)	2	24	4	33	4	37	4	19	6	2	69	30	4	67	2	100	0	
Sporadic (%)	2	43	4	24	5	54	4	6	6	9	69	27	4	29	2	0	1	100
Elevated ALT (%)	1	83	3	63	3	31	2	59	4	69	33	84	4	60	1	100	2	52
Alcohol consumption >20 g/day (%)	1	56	4	21	4	26	4	2	5	29	66	19	3	0.8	2	8	2	0
Steatosis (%)	0		2	76	2	34	0		1	25	20	48	2	16	1	25	1	20
HIV (%)	1	0	2	0	3	0	2	0	6	21	60	0.2	4	1	1	9	2	0
HBV (HBsAg positive) (%)	1	0	2	0	4	0	2	0.1	6	2	62	0.2	3	0.8	1	0	3	4
HCV RNA positive (%)	2	100	4	97	6	82	4	100	6	91	66	97	4	79	2	96	4	99
Genotype 1 (%)	1	31	4	63	3	43	4	91	5	35	65	53	4	51	1	45	2	67
Genotype non-1 (%)	1	32	4	28	3	27	4	9	5	15	65	27	4	18	1	31	2	33
HAI	0		2	5.7	1	3.6	0		1	7.1	17	6.8	1	3.6	0		0	

*Mean age at HCV infection: calculated by taking the difference between the mean age at assessment of liver disease and the mean duration of HCV infection when direct information about age at infection was not available. Abbreviations: IDUs, injecting/intravenous drug users; HCV, hepatitis C virus; BMI, body mass index; ALT, alanine aminotransferase; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; RNA, ribonucleic acid; HAI, histological activity index.

timates for all stages than those who acquired HCV at a younger age (<30 years). Estimates for individuals who had longer duration of HCV infection (>20 years) were lower than those who had shorter duration of infection (<20 years). Studies published prior to the year 2000 appeared to have higher estimates than those published in the year 2000 and after.

Visual examination of the funnel plots of the log stage-specific transition probabilities against the study size of all studies included in the meta-analysis revealed symmetry of the individual studies to the pooled mean estimates, except for transition from fibrosis stage 1 to 2 (Supplementary Figs. 3A-D and 4). Sensitivity analyses showed that the pooled estimates were in general robust to the exclusion of any one study from the meta-analysis, removal of studies at the extremes of the plot, or omission of 16 studies that collectively reported adjacent fibrosis stages. The total number of individuals with chronic HCV infection after omitting these 16 studies from the analysis was 29,343. The pooled (95% CI) stage-specific transition probabilities per year for the 95 reports were the following: F0→F1 0.119 (0.106-0.134); F1→F2 0.080 (0.070-0.091); F2→F3 0.117 (0.105-0.130); and F3→F4 0.116 (0.102-0.130). Analyses of studies without covariates would have resulted in higher estimates, but the pattern of the effect remained the same.

The pooled estimates derived from the indirect method (stage-constant estimate) were: for the fixed effects model, 0.082 (95% CI, 0.081-0.083) per year; and for the random effects model, 0.103 (95% CI, 0.098-0.108).

Predicted Cumulative Probability of Cirrhosis. Comparisons of predicted cumulative probability of cirrhosis between stage-specific (MMLE) and stage-constant (indirect) methods, study designs, settings, and selected populations are shown in Fig. 2A-F. These estimates are derived from the unadjusted transition probabilities. For all studies, the 20-year and 30-year predicted cumulative probability of cirrhosis using the stage-specific transition probabilities were 16% (95% CI, 14%-19%) and 41% (36%-45%), respectively. The corresponding estimates using the stage-constant estimates were 14% (13%-15%) and 37% (35%-39%), respectively. The results from the two approaches did not appear to be substantially different, with an absolute difference of 2% at 20 years and 4% at 30 years (Fig. 2A).

The 20-year predicted estimates of cirrhosis vary by study design, setting, and population, and by different age at HCV infection and duration of infection (Fig. 2B-F). Compared to cross-sectional/retrospective studies, the predicted estimates were lower for retrospective-prospective studies (18%, 15%-21% versus 7%, 4%-14%) (Fig. 2B). Similarly, the predicted estimates of cirrhosis for

Table 4. Annual Stage-Specific Transition Probabilities in Individuals with Chronic Hepatitis C Virus Infection (MMLE Method)

Fibrosis Stage	Fixed Effects	Model Meta-Analysis	Random Effects	Model Meta-Analysis	Random Effects	Model Meta-Regression
	Estimate	Mean (95% CI)	Estimate	Mean (95% CI)	Estimate	Mean (95% CI)*
All studies						
F0→F1†	0.109	(0.107, 0.110)	0.117	(0.104, 0.130)	0.117	(0.107, 0.127)
F1→F2†	0.068	(0.067, 0.069)	0.085	(0.075, 0.096)	0.085	(0.078, 0.093)
F2→F3†	0.113	(0.110, 0.116)	0.120	(0.109, 0.133)	0.121	(0.112, 0.130)
F3→F4†	0.125	(0.120, 0.130)	0.116	(0.104, 0.129)	0.115	(0.107, 0.123)
Cross-sectional/retrospective						
F0→F1†	0.115	(0.113, 0.117)	0.124	(0.111, 0.139)	0.124	(0.115, 0.135)
F1→F2†	0.067	(0.066, 0.068)	0.088	(0.075, 0.098)	0.086	(0.079, 0.094)
F2→F3†	0.113	(0.110, 0.116)	0.123	(0.111, 0.136)	0.124	(0.115, 0.133)
F3→F4†	0.125	(0.120, 0.130)	0.119	(0.107, 0.134)	0.119	(0.111, 0.127)
Retrospective-prospective						
F0→F1†	0.063	(0.060, 0.066)	0.065	(0.046, 0.091)	0.065	(0.046, 0.092)
F1→F2†	0.090	(0.084, 0.097)	0.077	(0.052, 0.113)	0.075	(0.049, 0.115)
F2→F3†	0.109	(0.098, 0.120)	0.098	(0.067, 0.142)	0.105	(0.067, 0.164)
F3→F4†	0.127	(0.109, 0.148)	0.082	(0.051, 0.133)	0.080	(0.049, 0.132)
Clinical setting						
F0→F1†	0.114	(0.112, 0.116)	0.123	(0.110, 0.138)	0.123	(0.114, 0.134)
F1→F2†	0.069	(0.068, 0.071)	0.090	(0.078, 0.103)	0.090	(0.082, 0.099)
F2→F3†	0.113	(0.110, 0.117)	0.123	(0.111, 0.137)	0.125	(0.115, 0.135)
F3→F4†	0.127	(0.122, 0.132)	0.121	(0.108-0.135)	0.120	(0.113, 0.128)
Nonclinical setting						
F0→F1†	0.079	(0.076, 0.083)	0.079	(0.053, 0.117)	0.079	(0.052, 0.119)
F1→F2†	0.060	(0.056, 0.063)	0.060	(0.051, 0.071)	0.059	(0.048, 0.072)
F2→F3†	0.109	(0.099, 0.119)	0.100	(0.076, 0.133)	0.108	(0.077, 0.152)
F3→F4†	0.112	(0.097, 0.129)	0.081	(0.051, 0.129)	0.077	(0.047, 0.127)

Hepatic fibrosis stage based on METAVIR fibrosis scoring system:¹² F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; and F4, cirrhosis. *Adjusted for study design and population, publication year, age at hepatitis C virus infection (mean 25.5 years), duration of infection (17.5 years), male gender (62%), injecting/intravenous drug use (41%), blood transfusion (31%), excess alcohol consumption (19%), HIV positivity (2%), HCV RNA positivity (95%), and genotype 1 (54%) (Tables 2 and 6). †F0→F1, F1→F2, F2→F3, and F3→F4: stage-specific transition probabilities. Abbreviation: MMLE, Markov maximum likelihood estimation.

nonclinical setting—based studies were lower compared to clinical setting—based studies (7%, 4%-12% versus 18%, 16%-21%) (Fig. 2C). The predicted estimates of cirrhosis were much higher for dialysis patients and renal transplant recipients compared to other populations (Fig. 2D). Individuals who acquired the infection at an older age (> 30 years) were approximately two to three times as likely to progress to cirrhosis at 20 years than those who acquired infection at a younger age (<30 years) (Fig. 2E). Estimates for individuals who had a shorter duration of infection (<10 years), were much higher than those who had a longer duration of infection (> 10 years). Estimates of cirrhosis were lower for studies published in the year 2000 and after compared to those published prior to the year 2000 (15%, 13%-18% versus 33%, 20%-58%).

Impact of Covariates on Fibrosis Progression. In the univariate regression (Supplementary Appendix E), most covariates were significantly associated with fibrosis progression except male gender, HIV positivity, and excess alcohol use. In the meta-regression (Table 6), duration of HCV infection was independently associated with all stages of fibrosis progression. Based on the backward regression, we established final models for each stage pro-

gression (Table 7). In the final model, we could create regression equations that could be used to calculate stage-specific progression rates and risk of cirrhosis for a cohort of patients or an individual. For example, for a cohort of male patients with IDU acquisition, a mean age at HCV acquisition of 25 years, mean duration of HCV infection of 20 years, excess alcohol consumption, genotype 1, and identified in a clinical setting, the mean progression rates would be as follows: 0.109 (F0 to F1); 0.140 (F1 to F2); 0.148 (F2 to F3); and 0.084 (F3 to F4). Given a set of stage-specific rates, the total time required to reach cirrhosis stage could be calculated by using this formula:

$$T = \frac{1}{0.1} + \frac{1}{0.12} + \frac{1}{0.23} + \frac{1}{0.34}$$

Thus, for this cohort, the estimated number of years required to progress from infection (F0) to cirrhosis is 35 years, and risk of cirrhosis after 20 years of HCV infection is 20%. For a similar patient cohort without excess alcohol consumption, the estimates are 0.109, 0.063, 0.094, and 0.084, respectively, with an estimated time of 47.6 years required to progress from F0 to cirrhosis, and 20-year risk of cirrhosis of 8.5%.

Table 5. Annual Stage-Specific Transition Probabilities in Individuals with Chronic Hepatitis C Virus Infection by Study Population

Study Characteristic	Number of Studies	F0→F1 Mean (95% CI)*	F1→F2 Mean (95% CI)*	F2→F3 Mean (95% CI)*	F3→F4 Mean (95% CI)*
Study population					
Blood donors	2	0.083 (0.001-14.36)	0.041 (0.001-1.256)	0.112 (0.012-1.077)	0.074 (0.002-3.071)
Community	4	0.124 (0.062-0.246)	0.073 (0.048-0.110)	0.123 (0.082-0.185)	0.165 (0.126-0.217)
Dialysis patients	6	0.169 (0.064-0.448)	0.134 (0.044-0.411)	0.220 (0.131-0.369)	0.156 (0.073-0.334)
Females†	4	0.055 (0.029-0.107)	0.051 (0.042-0.063)	0.070 (0.045-0.108)	0.048 (0.020-0.112)
Injecting drug users	6	0.116 (0.059-0.228)	0.085 (0.065-0.110)	0.085 (0.049-0.147)	0.130 (0.053-0.319)
Liver clinic	79	0.116 (0.103-0.131)	0.082 (0.071-0.094)	0.119 (0.106-0.133)	0.117 (0.104-0.132)
Pediatric population	4	0.142 (0.049-0.414)	0.162 (0.051-0.517)	0.161 (0.063-0.414)	0.103 (0.041-0.258)
Post-transfusion	2	0.076 (0.011-0.554)	0.095 (0.016-0.571)	0.108 (0.038-0.307)	0.134 (0.035-0.504)
Renal transplant recipients	4	0.177 (0.068-0.461)	0.139 (0.052-0.372)	0.191 (0.072-0.501)	0.105 (0.037-0.296)
Age at assessment (years)					
<40	22	0.151 (0.110-0.207)	0.115 (0.082-0.163)	0.142 (0.113-0.178)	0.129 (0.099-0.169)
40	89	0.110 (0.098-0.123)	0.079 (0.069-0.090)	0.116 (0.104-0.129)	0.113 (0.100-0.128)
Age at HCV infection (years)					
<20	9	0.107 (0.059-0.196)	0.087 (0.047-0.160)	0.140 (0.093-0.212)	0.109 (0.063-0.186)
20-<30	77	0.106 (0.094-0.120)	0.073 (0.064-0.084)	0.102 (0.092-0.113)	0.105 (0.092-0.120)
30	25	0.160 (0.125-0.205)	0.134 (0.103-0.175)	0.187 (0.156-0.225)	0.158 (0.133-0.187)
Duration of HCV infection (years)					
<10	7	0.314 (0.204-0.484)	0.322 (0.179-0.580)	0.220 (0.146-0.333)	0.151 (0.098-0.233)
10-<20	69	0.131 (0.115-0.148)	0.080 (0.069-0.093)	0.133 (0.119-0.150)	0.134 (0.117-0.150)
20	35	0.077 (0.067-0.088)	0.074 (0.064-0.086)	0.089 (0.077-0.103)	0.088 (0.075-0.104)
Publication year					
Before 2000	10	0.138 (0.084-0.229)	0.104 (0.057-0.192)	0.187 (0.127-0.276)	0.174 (0.113-0.269)
2000 and after	101	0.115 (0.102-0.129)	0.083 (0.073-0.094)	0.115 (0.104-0.127)	0.112 (0.100-0.125)

Estimates of transition probabilities are based on random effects model of meta-analysis. These estimates are unadjusted and could be confounded by the effects of study design for example. Hepatic fibrosis stage based on METAVIR fibrosis scoring system:¹² F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; and F4, cirrhosis. *F0→F1, F1→F2, F2→F3, F3→F4 are stage-specific transition probabilities. †Estimates after exclusion of Di Martino et al.,⁵⁰ which examined the effect of estrogen on liver fibrosis progression in HCV-infected females: F0→F1 0.043 (0.038-0.050); F1→F2 0.048 (0.037-0.062); F2→F3 0.065 (0.034-0.126); and F3→F4 0.039 (0.015-0.099).

Discussion

Our systematic review has demonstrated that liver fibrosis progression in chronic HCV infection appears to be nonlinear and that estimates of disease progression are significantly influenced by duration of infection. Overall, the predicted cumulative probability of cirrhosis at 20 years after the infection was 16% (95% CI, 14%-19%), and nearly three-fold higher at 30 years (41%, 36%-45%).

Our estimates are in agreement with previous studies^{6,7} with regard to the effects of different study designs, settings, and populations. In our study, higher transition rate estimates were found consistently across all stages in cross-sectional/retrospective studies than in retrospective-prospective studies. Similarly, studies conducted in clinical settings showed higher transition rate estimates compared to those conducted in nonclinical settings. However, in contrast to previous estimates,^{6,8} we found that fibrosis progression was not linear and that transition rate estimates were generally higher in the initial stage F0→F1 than the following stage, F1→F2. The highest rate was found in the pro-

gression from F2→F3. Cross-sectional/retrospective studies most clearly followed this pattern; retrospective-prospective studies showed a more steady rate of progression. Similarly, studies conducted in clinical settings showed nonlinear progression pattern, while those conducted in nonclinical settings showed a more linear progression pattern. Reasons for nonlinear fibrosis progression rates might also be that distinct histologic categories may not reflect equal increments of fibrosis. Studies published prior to the year 2000 appeared to have higher transition rate estimates than those published in the year 2000 and after. This may relate to broader referral patterns in later studies, particularly liver clinic studies. For IDUs who are identified in clinic/cross-sectional studies, one would use the clinic IDU data, but ideally it would be adjusted for study design.

Our estimates of progression to cirrhosis at 20 years after the infection for studies conducted in nonclinical settings (7%, 4%-12%) are also in agreement with the previous estimate by Freeman et al.⁶ (7%, 4%-10%). However, our 20-year cirrhosis estimate was much

Table 6. Meta-Regression of Covariates Associated with Hepatic Fibrosis Progression in Chronic Hepatitis C Virus Infection

Covariates	F0→F1*				F1→F2*				F2→F3*				F3→F4*			
	SE	P Value	RR		SE	P Value	RR		SE	P Value	RR		SE	P Value	RR	
Intercept	-1.677	0.664	0.013		-2.356	0.818	0.005		-1.112	0.590	0.062		-2.322	0.773	0.003	
Study design																
Cross-sectional (reference)	—	—	—	1.00	—	—	—	1.00	—	—	—	1.00	—	—	—	1.00
Retrospective-prospective	-0.248	0.175	0.160	0.78	0.215	0.217	0.323	1.24	0.150	0.157	0.341	1.16	0.148	0.203	0.467	1.16
Study population																
Liver clinic (reference)	—	—	—	1.00	—	—	—	1.00	—	—	—	1.00	—	—	—	1.00
Blood donors	-0.062	0.331	0.852	0.94	-0.658	0.419	0.120	0.52	-0.043	0.340	0.899	0.96	-0.345	0.425	0.420	0.71
Community	0.346	0.224	0.127	1.41	0.118	0.274	0.668	1.13	0.214	0.187	0.256	1.24	0.386	0.226	0.090	1.47
Dialysis patients	-0.077	0.198	0.699	0.93	-0.147	0.243	0.548	0.86	0.072	0.214	0.737	1.07	0.203	0.283	0.476	1.22
Females	0.134	0.367	0.716	1.14	0.036	0.449	0.936	1.04	-0.350	0.323	0.281	0.70	-0.337	0.424	0.429	0.71
Injecting drug users	-0.065	0.326	0.842	0.94	-0.100	0.400	0.803	0.90	-0.140	0.291	0.631	0.87	0.296	0.382	0.441	1.34
Pediatric population	-0.112	0.512	0.827	0.89	1.817	0.627	0.005	6.16	0.104	0.461	0.821	1.11	-0.705	0.628	0.265	0.49
Posttransfusion	0.416	0.429	0.335	1.52	1.125	0.525	0.035	3.08	0.114	0.363	0.755	1.12	-0.457	0.451	0.314	0.63
Renal transplant recipients	-0.316	0.236	0.184	0.73	0.236	0.294	0.425	1.27	0.111	0.247	0.654	1.12	-0.390	0.386	0.315	0.68
Publication year																
Before 2000 (reference)	—	—	—	1.00	—	—	—	1.00	—	—	—	1.00	—	—	—	1.00
2000 and after	0.074	0.147	0.616	1.08	0.031	0.183	0.866	1.03	-0.108	0.133	0.418	0.90	-0.270	0.163	0.102	0.76
Gender: male†	0.870	0.478	0.072	2.39	0.393	0.579	0.499	1.48	0.037	0.424	0.931	1.04	0.342	0.553	0.538	1.41
Age at HCV infection	0.005	0.013	0.729	1.00	0.054	0.016	0.002	1.06	0.016	0.012	0.185	1.02	0.002	0.015	0.913	1.00
Duration of infection	-0.084	0.011	<0.0001	0.92	-0.040	0.014	0.005	0.96	-0.051	0.010	<0.0001	0.95	-0.038	0.013	0.004	0.96
Injecting drug use†	0.014	0.283	0.962	1.01	0.143	0.346	0.681	1.15	-0.408	0.249	0.105	0.66	0.262	0.316	0.410	1.30
Blood transfusion†	0.194	0.335	0.565	1.21	-0.548	0.411	0.186	0.58	0.085	0.292	0.772	1.09	1.308	0.368	0.001	3.70
Excess alcohol use†	-0.225	0.321	0.486	0.80	1.081	0.391	0.007	2.95	0.446	0.280	0.115	1.56	-0.315	0.355	0.378	0.73
HIV positive†	-0.064	1.156	0.956	0.94	-0.366	1.414	0.797	0.69	-0.549	1.030	0.595	0.58	-0.366	1.391	0.793	0.69
HCV RNA positive†	0.029	0.414	0.945	1.03	-1.243	0.510	0.017	0.29	-0.227	0.383	0.554	0.80	0.696	0.524	0.187	2.01
Genotype 1†	0.466	0.278	0.097	1.59	-0.095	0.341	0.781	0.91	-0.303	0.233	0.197	0.74	-0.533	0.291	0.071	0.59

Linear mixed model-maximum likelihood method. *Log stage-specific transition probabilities. †Proportion. Abbreviations: β , coefficient; SE, standard error; RR, relative risk; HCV, hepatitis C virus; RNA, ribonucleic acid. Values in bold indicate statistical significance.

lower for liver clinic populations (16%, 13%-19% versus 24%, 11%-37%). The results from the two approaches (that is, stage-specific and stage-constant) did not appear to be substantially different in the mid-term, but may differ in the very long-term.

There are a number of potential limitations relating to our methodology used in the meta-analysis. First, the concept of dynamic fibrosis progression restricts the analyses to individuals with a known or estimated duration of HCV infection and studies that reported intermediate stages of fibrosis F0 to F4. As a result, a number of earlier natural history studies^{5,34-39} that used a conventional method⁴⁰ of histological classification (that is, chronic persistent hepatitis, chronic active hepatitis) were not included in the analysis. Second, estimation of duration of HCV infection was according to patient self-report of the known date of first transfusion of blood or blood product, the first year of IDU, or the date of a single specific and convincing parenteral exposure. The accuracy of this commonly used approach may differ by mode of HCV acquisition. Exclusion of studies without known duration of infection would also mean that our estimates may not be generalizable to other populations without known risk

factors. Third, estimates derived from the MMLE method are sensitive to the completeness of fibrosis stage data and the accuracy of stage classification. Biased estimates may result from nonrandom missing data and/or misclassification.¹⁵ Additionally, transition rate estimates derived from this method could be biased if the referring rates differ with the severity of liver disease. Fourthly, the requirement of individual patient data from the primary papers may introduce bias as some covariates were either not available for a number of studies or available for only a subgroup of individuals who underwent liver biopsy. Nevertheless, in the absence of individual patient data, meta-regression offers the best method to explain heterogeneity among study results.⁴¹ Finally, our meta-regression model may be underpowered and may miss some predictors of fibrosis progression.

Our study also has significant strengths, improving on previous studies in a number of ways: (1) it is more comprehensive, including over 100 English and non-English language studies; (2) it uses the Markov maximum likelihood method to estimate prognosis, which does not require the assumption of constant progression rates for each stage; and (3) it allows estimation of the effects of

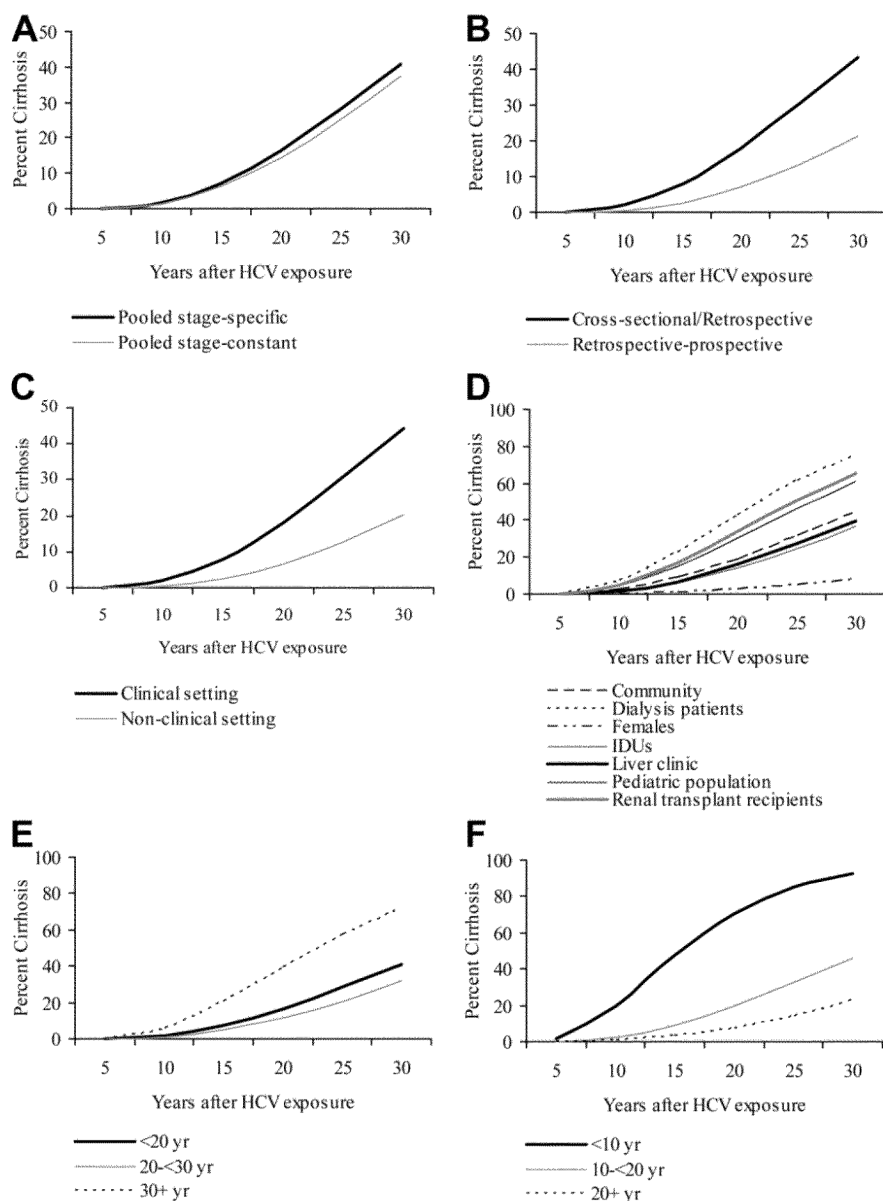


Fig. 2. Comparison of predicted cumulative rates of cirrhosis by: (A) transition probability estimation method; (B) study design; (C) setting; (D) selected study population; (E) age at HCV infection; and (F) duration of HCV infection. HCV, hepatitis C virus; IDUs, injecting/intravenous drug users. Note: Projections are based on unadjusted transition probabilities and may be confounded by the effects of other covariates; for example, study design.

study design, setting and population and clinical factors on disease progression.

Older age at infection, duration of infection, male gender, alcohol consumption >50 g/d, and HIV coinfection are well established factors associated with fibrosis progression.⁶ Our analysis found similar results. Additionally, in our final model, we found that study design factors, mode of HCV acquisition, and genotype 1 influenced fibrosis progression. The prevalence of HIV coinfection was low (2%) in our study population as most studies excluded this condition. Duration of infection was the most consistent factor significantly associated with progression of fibrosis. In our analysis, the majority (104/111) of studies had a duration of

infection of 10 or more years, of which 35 had 20 or more years.

In summary, we have produced more precise estimates of HCV-related fibrosis progression with adjustments for bias attributable to study design, and adjustments for selection factors associated with study population and clinical characteristics. The stage-specific estimates of disease progression support a nonlinear disease progression with cirrhosis risk particularly high in the third decade of HCV infection. In addition, we created an algorithm to estimate stage-specific progression rates and risk of developing cirrhosis for a cohort of patients with similar characteristics. Our estimates should provide more accurate prediction of

Table 7. Algorithm to Estimate the Risk of Cirrhosis of Individuals with Chronic Hepatitis C Virus Infection

Stage	Regression Equations	Value Range of Factors in the Equation
F0 to F1	$\exp[-2.0124 - (0.07589 \text{ duration}) (0.3247 \text{ design}) (0.5063 \text{ male proportion}) (0.4839 \text{ genotype 1 proportion})]$	Duration of HCV infection (years). Study design: cross-sectional/retrospective 1; retrospective-prospective 0.
F1 to F2	$\exp[-1.5387 - (0.06146 \text{ duration}) (0.8001 \text{ excess alcohol proportion})]$	Male proportion: 0 to 1.
F2 to F3	$\exp[-1.6038 (0.0172 \text{ age at HCV}) - (0.05939 \text{ duration}) (0.4539 \text{ excess alcohol proportion})]$	Genotype 1 proportion: 0 to 1. Age at HCV acquisition (years). Excess alcohol proportion: 0 to 1.
F3 to F4	$\exp[-2.2898 (0.01689 \text{ age at HCV}) - (0.03694 \text{ duration}) (0.5963 \text{ IDU proportion}) - (1.1682 * \text{blood transfusion proportion}) - (0.4652 \text{ genotype 1 proportion})]$	Risk of HCV acquisition: IDU proportion, 0 to 1; blood transfusion proportion, 0 to 1.

Abbreviations: exp, exponential function; HCV, hepatitis C virus; IDU, injection drug use.

HCV disease burden and cost-effectiveness analyses of antiviral therapies and preventive strategies.

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