Estimating Progression to Cirrhosis in Chronic Hepatitis C Virus Infection

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To gain a clearer understanding of the rate of progression to cirrhosis and its determinants in chronic hepatitis C virus (HCV) infection, a systematic review of published epidemiologic studies that incorporated assessment for cirrhosis has been undertaken. Inclusion criteria were more than 20 cases of chronic HCV infection, and information on either age of subjects or duration of infection. Of 145 studies examined, 57 fulfilled the inclusion criteria. Least-squares linear regression was employed to estimate rates of progression to cirrhosis, and to examine for factors associated with more rapid disease progression in 4 broad study categories: 1) liver clinic series (number of studies = 33); 2) posttransfusion cohorts (n = 5); 3) blood donor series (n = 10); and 4) community-based cohorts (n = 9). Estimates of progression to cirrhosis after 20 years of chronic HCV infection were 22% (95% CI, 18%-26%) for liver clinic series, 24% (11%-37%) for posttransfusion cohorts, 4% (1%-7%) for blood donor series, and 7% (4%-10%) for community-based cohorts. Factors that were associated with more rapid disease progression included older age at HCV infection, male gender, and heavy alcohol intake. Even after accounting for these factors, progression estimates were much higher for cross-sectional liver clinic series. Selection biases probably explain the higher estimates of disease progression in this group of studies. Community-based cohort studies are likely to provide a more representative basis for estimating disease progression at a population level. These suggest that for persons who acquire HCV infection in young adulthood, less than 10% are estimated to develop cirrhosis within 20 years. (HEPATOLOGY 2001;34:809-816.)

The majority of persons with hepatitis C virus (HCV) infection progress to chronic infection, which can lead to liver fibrosis and the subsequent occurrence of cirrhosis, liver failure, and hepatocellular carcinoma.[1] However, it is unclear what proportion of persons will develop HCV-related hepatic complications and who is most at risk of progression. The likelihood of progression can influence choice about therapy for the individual, and is a fundamental factor in predicting disease burden at a population level.

Because chronic HCV infection is largely asymptomatic and runs a protracted and highly variable course, it has been difficult to reliably measure disease progression in epidemiologic studies.[2] Early studies in blood-transfusion recipients and liver clinic patients seemed to indicate that cirrhosis would develop in 20% to 50% within 20 years of acquiring HCV infection.[3,4] Then, several more recent studies suggested progression rates that were much lower, of the order of 2% to 10%.[5-9] Some interpreted these discrepancies as being caused by different distributions of factors associated with more rapid disease progression, such as age at HCV infection, gender, and source of HCV infection, between the study populations. The higher estimates, however, continue to be used to project disease burden at a population level.[10]

To try to gain a better understanding of the course of disease in chronic HCV infection, including the impact of different methodologic designs on disease progression estimates, we undertook a systematic review of available published studies of HCV natural history.

PATIENTS AND METHODS

The MEDLINE database to the end of 2000 was searched for English-language articles using "hepatitis C," "cirrhosis," and "fibrosis" as keywords. Papers cited in the bibliographies of primary articles were also reviewed. Data relating to persons with chronic HCV infection who had undergone assessment of stage of chronic liver disease were extracted. Definitions of chronic HCV infection were based on the presence of anti-HCV antibody and one or a combination of either: 1) consistent histopathology on liver biopsy; 2) an elevated alanine transaminase (ALT) level, without an alternative cause of chronic liver disease; 3) the presence of HCV RNA as detected by polymerase chain reaction; or 4) recombinant immunoblot assay positivity. Studies were excluded if they reported fewer than 20 cases of chronic HCV infection, or if they gave no information regarding either the age of subjects or the duration of infection.

Based on the method of recruitment, the studies were divided into 4 groups: cross-sectional series of persons referred to specialist liver clinics (liver clinic series), longitudinal studies of persons with posttransfusion hepatitis (posttransfusion cohorts), cross-sectional series of persons newly diagnosed with chronic HCV infection at blood donor screening (blood donor series), and predominantly longitudinal community-based studies (community-based cohorts). The post-

Abbreviations: HCV, hepatitis C virus; ALT, alanine transaminase; HIV, human immunodeficiency virus.

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transfusion cohorts were based on persons with posttransfusion non-A, non-B hepatitis (defined by persisting ALT elevation following transfusion, in the absence of an alternative cause), subsequently found to have chronic HCV infection when diagnostic antibody testing became available. The community-based cohorts consisted of series of patients followed up after acute infection, studies of women infected after exposure to contaminated immunoglobulin, population-based assessments of chronic liver disease in regions of high HCV prevalence, and a prospective study of injecting-drug users with HCV infection.

The 2 factors on which our estimation of disease progression in chronic HCV infection were based were reported prevalence of cirrhosis and duration of HCV infection. Assessment of liver disease stage was generally by histopathologic examination of liver tissue at the latest follow-up point in longitudinal studies and at recruitment in cross-sectional studies. Although different fibrosis staging systems were employed, cirrhosis was defined on the basis of well-established histopathologic criteria (bridging fibrosis and nodule formation).[11] In those studies that also used nonhistopathologic criteria, these were based on clinical, laboratory, and ultrasound evidence consistent with cirrhosis.[12]

For each study, mean duration of HCV infection was abstracted when available. In those studies not reporting mean duration of HCV infection, it was estimated using the following method. For those studies that reported both the mean age at assessment of liver disease and the mean duration of HCV infection, the mean age at HCV acquisition was calculated. Within each study category, these were averaged to give an unweighted mean age at HCV acquisition. For those studies that only provided data regarding the age at assessment of liver disease, the study-category mean age at HCV acquisition was subtracted from the individual-study mean age at assessment to give an estimate of the duration of HCV infection. For example, the duration of HCV infection for a study with a mean age at assessment of liver disease stage of 40 years, within a study category with an estimated mean age at HCV infection of 25 years, would be 15 years.

For each of the 4 study categories, rates of progression to cirrhosis were graphically assessed by plotting prevalence of cirrhosis against estimated duration of chronic HCV infection for each study. Individual study 95% CIs for cirrhosis prevalence were calculated based on binomial distributions, and excluded patients lost to follow-up in longitudinal studies. To model the rate of progression to cirrhosis for each study category, least-squares linear regression lines with 95% CIs, based on the estimated standard error of the slopes of the regression lines, were fitted. Both unweighted and weighted (according to study sample size) analyses were performed. As a further sensitivity analysis, exponentially increasing lines were also fitted using least squares.

The impact of factors previously identified as influencing disease progression (age at infection, gender, alcohol consumption, ALT level) on the rate of progression to cirrhosis was also assessed by plotting individual study estimates of cirrhosis prevalence at 20 years against each factor. For these analyses, cirrhosis prevalence at 20 years was estimated for each study based on a linear fibrosis progression rate. For example, a study with an estimated mean duration of HCV infection of 10 years and 5% cirrhosis prevalence would have an estimated 20-year cirrhosis prevalence of 10%. For each study category, the trend related to each factor was assessed using least-squares linear regression. Only studies that provided information regarding the factor in question were able to be included.

RESULTS

A total of 145 studies were reviewed. Fifty-nine reported fewer than 20 cases of chronic HCV infection, and 29 gave no information regarding either the age of subjects or the duration of infection. Fifty-seven studies published between 1990 and 2000 fulfilled the inclusion criteria and were included in the analysis (Table 1). The majority (n = 33) were cross-sectional series of persons referred to specialist liver clinics (Table 2). Liver clinic series also had the largest mean study population (n = 482) (Table 2). In all 4 study categories, there was a majority of men; however, the proportion of women was close to 50% in the blood donor series and community-based cohorts (Table 2). The basis on which chronic HCV infection was diagnosed varied across study categories, with blood donor series (67%) and community-based cohorts (43%) employing HCV-RNA polymerase chain reaction testing in a large proportion of cases. Liver clinic series and posttransfusion cohorts were more likely to use elevated ALT levels and liver biopsy evidence of chronic infection. Staging of liver disease was on the basis of liver biopsy for all cases in blood donor series, 99% in liver clinic series, 90% in posttransfusion cohorts, and 59% in community-based cohorts.

The mean age at assessment of the stage of chronic liver disease was highest for posttransfusion cohorts (55 years), as was the estimated mean age at acquisition of HCV infection (42 years) (Table 2). The mode of HCV transmission varied significantly. Only in the community-based cohorts did the majority of subjects acquire HCV through injecting-drug use (Table 2). The proportion of subjects with an unknown risk factor was highest for the blood donor series. The proportion of subjects with an elevated ALT level at the time of liver disease stage assessment was higher for liver clinic series (87%) than either blood donor series (67%) or community-based cohorts (63%).

The duration of chronic HCV infection required estimation (as outlined in Patients and Methods) in 60% (6 of 10) of blood donor series, 55% (18 of 33) of liver clinic series, 11% (1 of 9) of community-based cohorts, and 0% (0 of 5) of posttransfusion cohorts. The community-based cohorts involved longitudinal follow-up, apart from one study that comprised a large community-based (nonreferred) cross-sectional assessment of chronic liver disease.[61]

The modeled progression rates to cirrhosis based on unweighted analyses for the 4 study categories are outlined in Fig. 1. The estimated proportion with cirrhosis at 20 years among the community-based cohorts was 6.5% (3.5%-9.5%) (Fig. 1A). An analysis of disease progression excluding the 2 studies of women infected with HCV through contaminated anti-D immunoglobulin (and potentially biased as a result of the homogeneity of the study populations)[6,8] gave an estimated cirrhosis prevalence after 20 years of 7.8% (95% CI, 4.9%-10.6%). For the posttransfusion cohorts, the estimated proportion with cirrhosis at 20 years was 23.8% (11.0%-36.6%) (Fig. 1B).

The estimated proportion of persons with cirrhosis at 20 years in the blood donor series was 3.7% (0.8%-6.5%) (Fig. 1C). In the liver clinic series, an estimated 21.9% (17.9%-25.9%) of persons with chronic HCV infection progressed to cirrhosis at 20 years (Fig. 1D). In these studies, the range of individual study cirrhosis prevalence was wide, with several study 95% CIs not falling within the 95% CIs for overall disease progression. This was particularly true for studies with an estimated mean duration of chronic HCV infection beyond 20 years, with a cirrhosis prevalence of less than 5% to greater than 50%.

The estimated 20-year cirrhosis rates based on weighted (according to study sample size) analyses were not significantly different to those from the unweighted estimates (Table 3). Similarly, analyses of disease progression based only on those studies not requiring our estimation of mean duration of

TABLE 1. Studies of Patients With Chronic HCV Infection

	Study Description*	Country	Population Size	Mean Age (yr)	Mean Duration (yr)	Estimated Duration† (yr)	Cirrhosis Prevalence
(Khan et al., 2000)[13]	Liver clinic	Australia	455	37	12		20.0%
(Roberts et al., 1993)[14]	Liver clinic	Australia	63	37	11		6.3%
(Strasser et al., 1995)[15]	Liver clinic	Australia	152	36	15		32.2%
(Ostapowicz et al., 1999)[16]	Liver clinic	Australia	346	35	15		12.0%
(Michielsen et al., 1997)[17]	Liver clinic	Belgium	51	47		18	16.4%
(Kleter et al., 1998)[18]	Liver clinic	Europe	292	49	11		23.3%
(Poynard et al., 1997) OBSVIRC[19]	Liver clinic	France	1,138	44	11		12.5%
(Poynard et al., 1997) DOSVIRC[19]	Liver clinic	France	607	46	14		17.1%
(Poynard et al., 1997) METAVIR[19]	Liver clinic	France	490	49		20	31.4%
(Roudot-Thoraval et al., 1997)[20]	Liver clinic	France	6,664	45	13		21.4%
(Pessione et al., 1998)[21]	Liver clinic	France	233	41		12	3.9%
(Serfaty et al., 1998)[22]	Liver clinic	France	668	56		17	15.4%
(Berg et al., 1997)[23]	Liver clinic	Germany	187	43		14	15.0%
(Niederau et al., 1998)[24]	Liver clinic	Germany	838	49	10		16.8%
(Tassopoulos et al., 1998)[25]	Liver clinic	Greece	152	43		14	18.4%
(Silini et al., 1995)[26]	Liver clinic	Italy	341	52		23	16.2%
(Benvegnu et al., 1997)[27]	Liver clinic	Italy	429	50		21	25.4%
(De Moliner et al., 1998)[28]	Liver clinic	Italy	96	47		18	16.7%
(Kiyosawa et al., 1990)[29]	Liver clinic	Japan	205	54		25	35.1%
(Hagiwara et al., 1993)[30]	Liver clinic	Japan	104	47		18	26.0%
(Takahashi et al., 1993)[31]	Liver clinic	Japan	333	49	19		17.4%
(Yano et al., 1993)[3]	Liver clinic	Japan	155		26		29.7%
(Vaquer et al., 1994)[32]	Liver clinic	Spain	29	44		15	6.9%
(Vaquer et al., 1994)[32]‡	Liver clinic	Spain				20	24.1%
(Lo Iacono et al., 1998)[33]	Liver clinic	Spain	253	43		14	6.3%
(Verbaan et al., 1998)[34]	Liver clinic	Sweden	106	43	14		19.0%
(Luo et al., 1998)[35]	Liver clinic	Taiwan	93	53		24	8.6%
(Healey et al., 1995)[36]	Liver clinic	UK	42	37	13		4.9%
(Simmonds et al., 1996)[37]	Liver clinic	Europe	610	49		20	22.5%
(Stanley et al., 1996)[38]	Liver clinic	UK	100	38		9	17.0%
(Wong et al., 1997)[39]	Liver clinic	UK	140	36	12		7.0%
(Tong et al., 1995)[4]	Liver clinic	USA	131	57	22		51.1%
(Gholson et al., 1997)[40]	Liver clinic	USA	50	51		22	2.0%
(Wiley et al., 1998)[41]	Liver clinic	USA	176	46	21		39.0%
(Tremolada et al., 1992)[42]	Post-transfusion	Italy	135	54	8		15.6%
(Gruber et al., 1993)[43]	Post-transfusion	Sweden	55	44	13		10.9%
(Seeff et al., 1992/1998)[44,45]	Post-transfusion	USA	76	49	18		15.0%
(Di Bisceglie et al., 1991)[46]	Post-transfusion	USA	39	62	10		20.5%
(Koretz et al., 1993)[47]	Post-transfusion	USA	55	65	14		19.5%
(Serfaty et al., 1995)[48]	Blood donors	France	85	39		17	7.0%
(Yuki et al., 1994)[49]	Blood donors	Japan	61	48		26	0.0%
(Esteban et al., 1991)[50]	Blood donors	Spain	77	45		23	9.0%
(Prieto et al., 1995)[51]	Blood donors	Spain	64	42		20	0.0%
(Munoz-Gomez et al., 1996)[52]	Blood donors	Spain	35	42	19		2.8%
(Salmeron et al., 1996)[53]	Blood donors	Spain	85	42		20	0.0%
(Shev et al., 1995)[54]	Blood donors	Sweden	62	34	12		4.8%
(Irving et al., 1994)[55]	Blood donors	UK	52	35		13	7.7%
(Conry-Cantilena et al., 1997)[56,57]	Blood donors	USA	81	37	15		5.0%
(Shakil et al., 1995)[58]	Blood donors	USA	51	39	19		2.0%
(Rodger et al., 1999/2000)[5,59]	Community	Australia	51	43	23		7.8%
(Wiese et al., 2000)[6]	Community	Germany	500	44	20		0.8%
(Vogt et al., 1999)[7]	Community	Germany	37	23	20		5.4%
(Kenny-Walsh, 1999)[8]	Community	Ireland	390	45	17		1.9%
(Bellentani et al., 1994)[60]	Community	Italy	199	40		14	11.1%
(Ohkoshi et al., 1995)[61]	Community	Japan	50	64	30		12.0%
(Mattsson et al., 1993)[62]	Community	Sweden	24	41	13		8.30%
(Thomas et al., 2000)[9]	Community	USA	722	43	23		6.5%
(Alter et al., 1992)[63]	Community	USA	106		3		1.0%

*Studies were grouped according to the 4 categories outlined in Patients and Methods.

†Duration of infection was estimated in the liver clinic, blood donor, and community series based on a mean age at HCV acquisition of 29 years, 22 years, and 26 years, respectively.

‡Vaquer et al. followed patients prospectively for 5 years.

TABLE 2. Summary of Studies of Patients With Chronic HCV Infection

Study Description	Number of Studies	Mean Subjects	Proportion		Cases of Cirrhosis	Mean Age (yr)		Mode of Acquisition			Elevated ALT	>30-50 g alc/d
			Male	Biopsied		Assessed	Infected	IDU	BT	Sporadic		
Liver clinic	33	482	62%	99%	3157	45	29	33%	32%	30%	87%	16%
Posttransfusion	5	72	67%	90%	57	55	42		100%*		100%*	
Blood donors	10	65	55%	100%	26	40	22	21%	25%	16%	67%	15%
Community	9	231	55%†	59%	95	46‡	26‡	57%	38%		62%	10%

NOTE. Data represent the unweighted mean from the included studies. Abbreviations: alc, alcohol; BT, blood transfusion; IDU, injecting-drug use.
*Patients were recruited on the basis of persistently abnormal liver function tests following blood transfusion.
†Excluding two series of women infected with contaminated anti-D immunoglobulin.[6,8]
‡Excluding a single series of infants infected during cardiac surgery.[7]

chronic HCV infection did not differ significantly from the analyses with all studies included (Table 3). Assuming an exponentially increasing cirrhosis prevalence over time, rather than linear disease progression, also did not significantly alter the estimates of cirrhosis prevalence after 20 years of infection (Table 3).

The impact of various cofactors on the rate of progression to cirrhosis was examined. Within each study category, older age at HCV infection was associated with increased cirrhosis prevalence at 20 years (Fig. 2). The study of HCV among infants transfused at the time of cardiac surgery was excluded from this analysis.[7] The 20-year estimated cirrhosis preva-

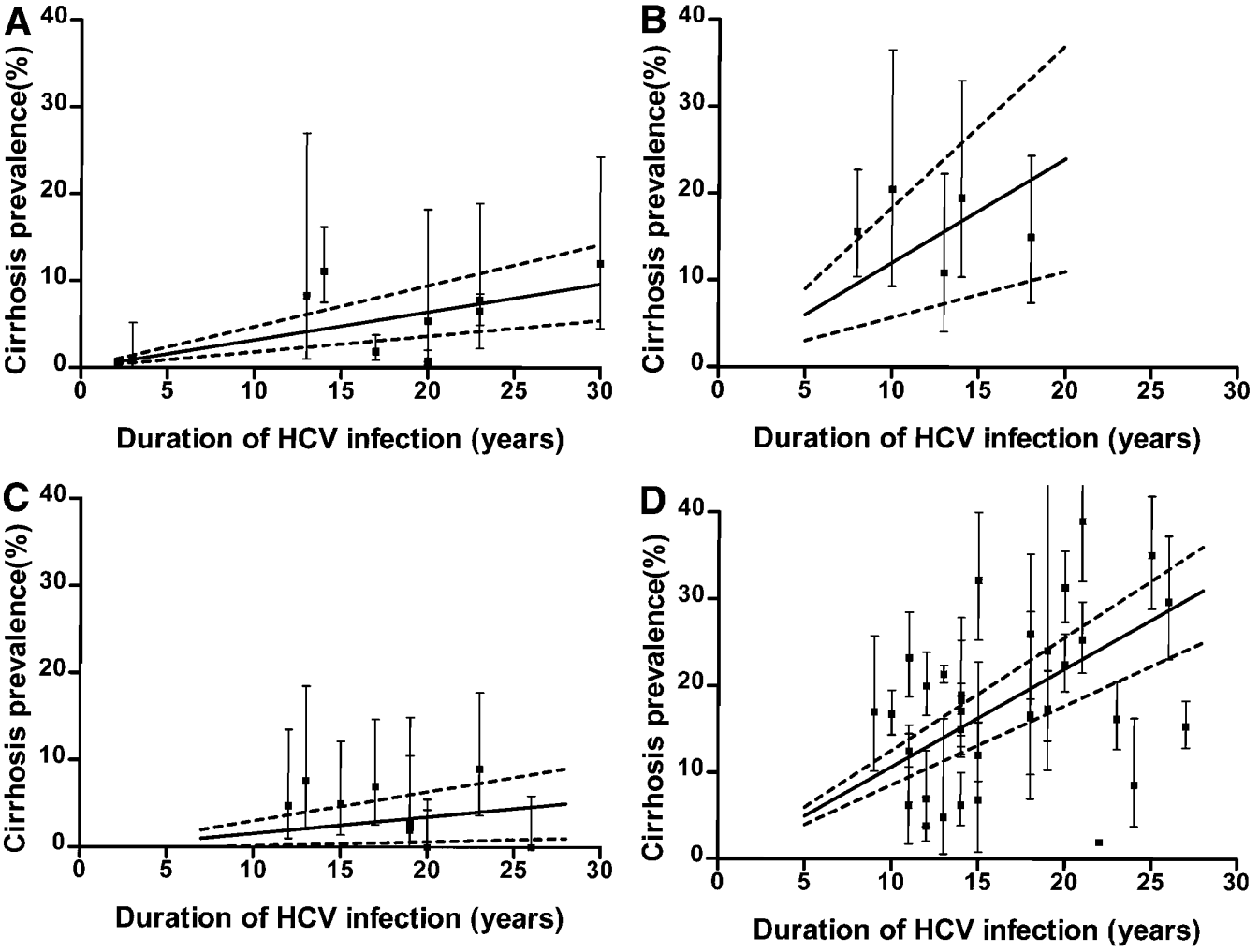

FIG. 1. Modeled rate of progression to cirrhosis among community-based cohorts (A), posttransfusion cohorts (B), blood donor series (C), and liver clinic series (D). Individual dot points correspond to cirrhosis prevalence at the estimated mean duration of infection for each individual study (Table 1). 95% CIs excluded patients lost to follow-up in longitudinal studies (A and B). *Solid lines* represent the mean rate of progression to cirrhosis for all of the studies within each study category. *Scored lines* represent 95% CIs for the modeled rate of progression. Studies were not weighted according to sample size.

TABLE 3. Sensitivity Analysis of the Estimates of Mean Prevalence of Cirrhosis After 20-Years HCV Infection for Each of the Study Categories

Study Description	Unweighted Analysis	Weighted Analysis*	Excluding Estimates†	Exponential Analysis‡	Study Categories Standardized			
					Mean Age at Infection 25	50% Male	10% >30-50 g alc/d	60% High ALT
Liver clinic	21.9% (17.9-25.9%)	25.0% (21.7-28.4%)	28.1% (22.1-33.9%)	21.5% (17.5-25.6%)	23.7%	19.1%	24.3%	15.8%
Posttransfusion	23.8% (11.0-36.6%)	23.8% (10.8-36.8%)	23.8% (11.0-36.6%)	24.6% (11.1-39.8%)	11.8%	21.7%		
Blood donors	3.7% (0.8-6.5%)	3.8% (0.9-6.8%)	4.1% (0.0-8.3%)	3.8% (1.1-6.6%)	7.4%	3.2%	2.6%	3.7%
Community	6.5% (3.5-9.5%)	4.7% (1.9-7.5%)	6.0% (3.4-8.5%)	6.4% (3.5-9.4%)	5.8%	7.8%	6.5%	5.2%

Abbreviation: alc, alcohol.

*Weighted according to study size.

†Excluding studies that did not provide duration of infection and in which estimates were made as outlined in Patients and Methods.

‡Assuming an exponentially increasing cirrhosis prevalence over time rather than linear disease progression.

lence was standardized around an age at infection of 25 years (Table 3); however, it was still significantly higher among the liver clinic series (23.7%) than the community-based cohorts (5.8%). In contrast, the age-at-infection–adjusted estimate for the posttransfusion cohorts declined to 11.8% (Table 3). Increased cirrhosis prevalence at 20 years was also associated with male gender within each category, but following standardization around a male proportion of 0.50, it remained disparate (Table 3). The studies of women infected with contaminated anti-D were excluded from this analysis.[6,8] Similarly, adjusting each study category to a mean proportion of 0.10 with heavy alcohol intake (>30 to 50 g daily) or a mean proportion of 0.60 with an elevated ALT did not completely correct the differences in cirrhosis prevalence seen between the study categories (Table 3).

DISCUSSION

This review has demonstrated that estimates of disease progression in chronic HCV infection are strongly influenced by study methodology and population sampling. Higher estimates arise from studies of persons with transfusion-acquired infection and those referred to specialist liver clinics, compared with those involving community-based cohorts and persons newly diagnosed at blood donor screening. Possible explanations for these disparate estimates are differences in prevalence of factors associated with more rapid disease progression across study types and inherent selection biases.

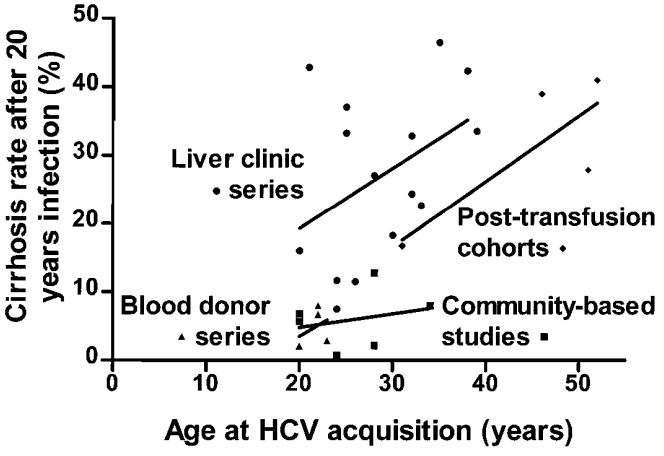

FIG. 2. Modeled impact of the age at infection on the rate of progression to cirrhosis for each study category. Individual dot points correspond to cirrhosis prevalence after 20-year HCV infection, assuming linear disease progression for each study. Only studies that gave information on the age at HCV infection were included. *Solid lines* represent the modeled impact of age at HCV acquisition within each study category.

Factors previously shown to influence disease progression in chronic HCV infection in individual studies have included older age at HCV infection, male gender, heavy alcohol intake,[19,20] coinfection with either hepatitis B or human immunodeficiency virus (HIV),[64,65] and the presence of an elevated ALT level.[66,67] Other than hepatitis B and HIV coinfection, as a result of exclusion of these cases from most series, each of these factors was found to be associated with higher estimates of disease progression in our modeling.

Age at HCV infection appears to account for a large component of the higher disease progression estimates for posttransfusion cohorts compared with the community-based cohorts and blood donor series, although there may be a role for other factors, such as other underlying chronic disease processes.

On the other hand, disease-progression estimates from the liver clinic series cannot be aligned with the community-based cohorts and blood donor series, even after taking into account age and other cofactors. For example, within the age at HCV-infection range of 20 to 30 years, the estimates from liver clinic series are some 3-fold higher than for the other 2 groups of studies. Furthermore, in a large liver clinic series, with a disease-progression estimate consistent with the overall category, even the group with no significant cofactors (women, infected at younger than 40 years of age, with low alcohol intake) had an estimated cirrhosis prevalence at 20 years of approximately 20%.[19]

If a difference in distribution of factors shown to influence disease progression does not explain the discrepancies in estimates of cirrhosis prevalence between liver clinic series and the community-based cohorts and blood donor series, are there alternative explanations? Liver clinics clearly recruit patients who, at the time of assessment for cirrhosis, had a higher prevalence of ALT elevation. It is therefore plausible that a proportion of these liver clinic patients had already developed cirrhosis and related symptoms, and were referred for assessment for these reasons. There would be a consequent under-representation of patients with less advanced disease in

the liver clinic series. By contrast, blood donors may be generally "healthier" and less likely to have developed HCV-related complications, giving an under-representation of persons with more advanced disease. These observations suggest that cross-sectional series of selected patients should not be used to predict the HCV-related disease burden at a population level.

It is likely that the community-based cohorts provide the most accurate estimates of progression to cirrhosis at a population level. With the exception of the 2 studies among women infected through contaminated anti-D immunoglobulin injections,[6,8] the community-based cohorts most closely represent HCV-infected populations in most industrialized countries: generally, young adulthood HCV infection, with injecting-drug use the predominant mode of HCV infection, and a significant proportion with normal ALT levels.[68] These studies indicate that persons who have been infected in early adulthood have a risk of progression to cirrhosis of less than 10% within 20 years of infection.

Because the natural history of chronic HCV infection is highly variable, and patients differ according to their duration of infection and presence of factors associated with more rapid disease progression, prognosis-based counseling must be individualized. Optimal determination of prognosis would involve assessment of disease-progression cofactors, an estimation of duration of HCV infection, and staging of liver disease. For example, a person who has been infected for an estimated 10 to 20 years and has both evidence of mild disease on liver biopsy and absence of cofactors clearly has a more favorable prognosis than the person who, over a similar duration of infection, has progressed to moderate-severe liver fibrosis. Consensus guidelines for antiviral therapy universally recommend intervention in the latter scenario, but many suggest ongoing clinical monitoring only for the former.[69] On the other hand, in many countries, current injecting-drug users are regularly tested for HCV infection, and diagnosis is commonly made at the primary care level in the first few years of infection. For these persons, particularly those without cofactors for more rapid disease progression (such as HIV coinfection), the community-based cohort estimates may be appropriate for providing broad prognostic messages.

There are a number of potential limitations in the methodology that we have employed in undertaking our review. Firstly, we have had to estimate the mean duration of chronic HCV infection for many of the studies, although in only one of the community-based cohorts. Separate analyses, excluding studies that required estimation of duration of chronic HCV infection, gave similar disease-progression estimates. Individual estimation of duration of infection is often problematic, but it is generally a problem of cross-sectional studies, rather than longitudinal studies. Secondly, 2 of the community-based cohorts studies were of women infected through contaminated anti-D immunoglobulin injections, the natural history of which may poorly represent disease progression generally in chronic HCV infection, but removing these 2 studies produced a very similar disease-progression estimate within this study category. Thirdly, the methods used to designate cirrhosis were not uniform across studies. However, across all study categories, the majority of cases of cirrhosis were diagnosed after assessment of liver biopsy histology. Finally, the majority of studies in each category reported a mean duration of infection of less than 20 years, and based on preliminary evidence,[19] it was assumed that hepatic fibrosis progression was linear. While fitting an exponentially increasing regression gave similar estimates of cirrhosis rates after 20 years of infection, the situation in the third and fourth decades is less certain. A recently published 45-year follow-up study of 17 American male military recruits with HCV infection, however, demonstrated that only 2 (11.8%) had developed advanced liver disease.[70]

Estimates and projections of the HCV-related burden of disease, and cost-effectiveness assessments for both prevention and treatment strategies, require clear evidence for natural-history assumptions. Studies continue to use Markov-type models, based predominantly on posttransfusion cohorts, which employ estimates of progression to cirrhosis at 20 years above 20%.[10,71] It is likely that community-based cohorts provide greater validity for such assumptions. Continued follow-up of these cohorts beyond the second decade of infection is required to further examine disease progression and HCV-related excess mortality among persons with chronic HCV infection.

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