Systematic Review: Outcome of compensated cirrhosis due to chronic hepatitis C infection.

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Abstract

Background and Aims

Most studies evaluating chronic hepatitis C (HCV) natural history have taken the development of cirrhosis as an end-point. We performed a systematic review of the literature to establish the outcome of compensated HCV cirrhosis.

Methods

A systematic literature review was performed. Only data regarding HCV monoinfected patients were included. Weighted mean annual percentage rates for death/transplantation, decompensation of cirrhosis and development of HCC were calculated.

Results

Thirteen papers were included. Despite some heterogeneity, we extracted data relating to 2386 patients. In compensated HCV cirrhosis the estimated annual rate of death/transplantation is 4.58%, of decompensation is 6.37% per and of HCC is 3.36%. When compared to studies of untreated patients, studies that included treated patients reported significantly lower mean annual percentage rates of HCC (2.52% versus 4.79%, *P*=0.02), but not decompensation (5.34% versus 7.88%, *P*=0.026) and death/transplantation (3.79% versus 4.62%, *P*=0.25).

Conclusions

These rates highlight the need for continued vigilance for the occurrence of HCC while confirming the relatively slow progress of compensated HCV cirrhosis. Heterogeneity in reporting means that these data may underestimate the rate of disease progression, particularly HCC development. It will be important to ensure clearer distinction between treatment responses in future studies.

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Introduction

Chronic infection with hepatitis C virus (HCV) is a leading cause of liver disease with over 170 million infected individuals worldwide (1) . A recent meta-analysis indicates that approximately 20-30% (2) of patients will progress to cirrhosis over a period of 20 years, although the proportion who will develop cirrhosis over longer periods of follow up remains unclear. Once cirrhosis has developed complications including gastrointestinal bleeding, porto-systemic encephalopathy, ascites and hepatocellular carcinoma (HCC) are common. Most studies of the natural history of chronic HCV infection have examined the development of cirrhosis as an end-point and have investigated risk factors for the development of cirrhosis (3, 4). In addition a number of reports have charted the natural history of compensated cirrhosis due to chronic HCV infection and have documented the higher frequency of HCC in patients with HCV-related cirrhosis compared to cirrhosis associated with other aetiologies – in particular alcohol (5, 6). However the rate at which complications of cirrhosis from chronic HCV infection develop remains unclear and here we report the results of a systematic review of studies published over the last fourteen years that have examined the development of decompensation.

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Methods

On-Line searches & Manuscript Selection

Studies were retrieved from pubmed (www.nlm.nih.gov) using the following search terms. [Search ((natural history of Hepatitis C Cirrhosis) **NOT** (HIV) **NOT** (review)) **NOT** (transplant) **Limits**: Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Comparative Study, Multicenter Study, English, All Adult: 19+ years.]. Manuscripts were then reviewed and evaluated for inclusion in the analysis. The bibliographies of these manuscripts were also examined for relevant papers that had not been captured by the initial search strategy. The last search was performed on 10th April, 2010. Papers were excluded on the bases of relevance to this study (in particular clear

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discrimination between decompensated and compensated cirrhosis) and the inclusion of patients with other causes of chronic liver disease without clear reporting of outcome in patients with HCV alone.

Data Analyses

Published data were entered into a Microsoft Excel spreadsheet and analysed. Where studies reported data on patients with co-infection or with other aetiologies for cirrhosis, only data from HCV mono-infected patients were included for further analysis.

Unless reported by the authors, annual percentage rates were calculated as the percentage of patients who reached an endpoint (for example death or development of a complication) in each study divided by the average (whether mean or median) duration of follow-up in years. Where not otherwise stated mean percentage rates for all studies were calculated by first multiplying each study's annual percentage rate by the number of patients in that study and then dividing by the total number of patients.

Student's t-test or the Mann-Whitney test was used for comparison of continuous variables. All reported *P* values are 2-sided, and a *P* value of less than 0.05 was considered significant.

Results

Searches and study characteristics

Using the search strategy described above, approximately 30 papers were considered. Following review thirteen papers met the entry criteria and were included in analyses (summarised in Table 1). Two groups (Fattovich *et al* and Bruno *et al*) have each published more than one study which satisfied

the entry criteria, however the degree of patient overlap between these studies could not be clearly ascertained. The most relevant study from each group was therefore included (7, 8), whilst the remaining papers were excluded from further analysis (9-11).

The most frequent study design was prospective cohort study (ten reports), although two retrospective cohort studies (8, 12) and one non-randomised controlled trial (13) were also identified. Two of the prospective cohort studies (14, 15), one retrospective cohort study (12) and the controlled trial (13) were designed to investigate the impact of interferon (IFN) therapy on the outcome of HCV cirrhosis; only data from the untreated or control groups who did not receive IFN therapy are included in the present analysis. Two prospective (16, 17) and one retrospective study (8) compared the outcome of patients with HBV and HCV cirrhosis, and one prospective study compared outcome of patients with HCV and alcohol-related cirrhosis [6]. Only the data pertaining to patients with HCV cirrhosis are included in Table 1.

The majority (eight) of investigations were conducted in Western Europe, one was performed in the USA (18) and four in Japan (6, 12, 15, 16). The number of participants was variable (median 144 patients), ranging from 55 (in the untreated cohort of one of the retrospective studies (12)) to 490 (16). Follow-up periods varied from mean 2.8 (14) to median 14.4 (7) years.

The outcomes assessed were reasonably uniform, with most studies evaluating rates of death, development of hepatocellular carcinoma (HCC), and decompensation of cirrhosis (including development of jaundice, ascites, variceal haemorrhage or hepatic encephalopathy). Two studies were designed to investigate the effect of interferon on development of HCC and so did not report data for other outcomes (12, 14). Transplantation was considered as an endpoint in seven studies, and was combined with death for the purposes of survival analysis.

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Inclusion and exclusion criteria from the studies are summarised in Table 2. All studies required a positive diagnosis based on the presence of HCV antibody, HCV RNA detection or both for inclusion. Cirrhosis was confirmed by biopsy in the majority of patients, or clinically diagnosed in a small minority based on a variety of criteria (varices or thrombocytopaenia with ultrasound markers of portal hypertension (13); presence of irregular liver margin on ultrasound, portal hypertension with laboratory evidence of chronic liver disease (17); or according to criteria described by Bonacini *et al*, (18, 19). Formal staging of cirrhosis as Child-Pugh A or B was required by eight studies. All of the studies excluded patients with signs of decompensation but in 4 papers this was not specifically stated (6, 14, 15, 21). However none of these studies had different outcomes suggesting that they too had in fact excluded patients with decompensated cirrhosis. Pre-existing HCC was generally an exclusion criterion, although this was not explicitly stated by Mazzella *et al* (14).

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All studies except three (14, 17, 20) excluded patients with other known causes for liver disease (including coexistent HBV infection). Four studies screened for HIV, and excluded co-infected patients. No study required participants to be abstinent from alcohol, and only six set a limit on alcohol consumption permitted for inclusion in the study.

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Patient characteristics

Data pertaining to 2328 patients was available from the thirteen studies meeting the inclusion criteria. The characteristics of the patients at entry to each study are summarised in Table 3. The mean age of participants was 58.2 years. The average ages of the patients in ten studies were relatively homogenous (54-61 years) but two studies described notably older (mean age 69) (6) and younger patients (mean age 52.1) (18). Gender distribution was more variable, ranging from 38% (6) to 75% (21) males. Baseline laboratory tests did not vary greatly between studies, presumably reflecting the

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requirement for compensated cirrhosis (Child-Pugh A or B) at enrolment. The presence of serum anti-HCV antibodies was used to diagnose HCV infection in eleven studies. The presence of serum HCV RNA diagnosed infection in the remaining two and was used to further confirm infection in seven studies. Three studies identified anti-HCV antibodies in the serum of participants, but did not confirm infection with RNA analysis (13, 14, 22). Whilst all patients enrolled in the studies conducted by Benvegnu *et al* and Serfaty *et al* were seropositive for HCV, not all patients included were HCV RNA positive (89% and 94% respectively) (17, 21). Stored serum samples were available for only 64% of the patients enrolled by Fattovich *et al* for HCV RNA testing, although HCV RNA was detected in all of these samples (8).

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In six studies a variable proportion of patients received treatment for HCV during the follow up period (11-59% of participants). All patients were treated with interferon, however the dose, regimen and treatment duration varied considerably between studies.

Outcomes

Table 4 summarises the available data on outcomes in patients with compensated HCV cirrhosis. Losses to follow up ranged from 3 to 57% of patients recruited and, broadly, the percentage of patients lost to follow up related to the length of the follow up period. Eight reports provide data on outcomes in HCV monoinfected, untreated patients (6-8, 12-16). Benvegnu *et al* (17) reported data on decompensation and HCC for HCV monoinfected patients (n=254), however figures for death/transplantation were only given for all patients, including those with HBV and HBV/HCV co-infection (a further 58 patients, total n=312). Similarly, the outcome data presented by Sangiovanni *et al* (20) included patients with other liver disease in addition to HCV (alcohol abuse, hereditary haemochromatosis and HBV, affecting 46 patients, or 21% of all those for whom data is presented in that study). Three further studies combined outcomes for both treated and untreated patients (18, 21,

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22) but detailed data on outcomes for those who did or did not receive therapy were not provided separately. Outcomes data for patients according to response to therapy are not provided.

Annual percentage rates of death/transplantation and decompensation of HCV cirrhosis are given in Table 5. Across the studies, the risk of the combined outcome of death/liver transplantation ranged from 2.74 to 6.72% per annum. The risk of developing any complication of cirrhosis was 2.77 - 11.70% per annum, with risk of HCC in particular ranging from 1.51-7.14% per annum. An estimate of mean annual percentage rates from all studies has been calculated by averaging the annual percentage rate data derived from each study. The results are shown in Table 5, final column. The overall estimated rate of death/transplant was 4.58% per annum, whilst the estimated rate of complications was 6.37% per annum.

To assess the impact of interferon therapy on the estimated annual percentage rates of death/transplantation, HCC or decompensation, we compared these rates in studies which did include patients treated with interferon versus those which did not. The mean annual percentage rate of HCC, but not that of death/transplant, was significantly lower in the studies where some participants received interferon (Figure 1). Although there was a trend towards a reduction in rate of decompensation amongst the studies including patients who had received interferon, this did not achieve statistical significance (mean 5.34 ± 0.79 versus 7.88 ± 1.88% per annum, p=0.26). These patients did not differ significantly in terms of age nor gender from those who had not received interferon (mean ages 56 ± 1.4 years and 59.5 ± 1.8 years respectively, p = 0.16; mean percentage of males 57.8 ± 4.6 and 50.6 ± 2.69 respectively, p= 0.14).

To assess the impact of ethnicity on outcomes in compensated HCC cirrhosis, we compared the average annual percentage rates of death/transplantation or HCC development between the Japanese

studies and the Western European studies included in this analysis. Only one Japanese study reported decompensation rates, so an average could not be calculated for this outcome. As none of the patients included in the Japanese studies had received interferon therapy, their average complication rates were compared with those of the four Western studies where the outcome data were available for untreated patients only. Whilst there was a trend for higher complication rates amongst the Japanese studies, this did not reach statistical significance (mean annual percentage rate of death/transplantation 5.62 ± 0.41 in Japanese versus 3.63 ± 0.16 in European studies, *P*=0.10; mean annual percentage rate of HCC 6.57 ± 0.49 in Japanese versus 4.27 ± 0.79 in European studies, *P*=0.07). Again, the patients included in these Japanese and European studies did not differ significantly in age or gender (data not shown).

Risk factors for disease progression

The majority of the studies included in the present analysis performed univariate and multivariate analyses to identify factors which independently increase risk of death/transplant, HCC or decompensation in HCV cirrhosis. Unfortunately direct comparison between reports was not possible due to differences in categorisation of the variables studied.

Considering all studies, multivariate analyses identified a total of 8, 9 and 14 different independent variables that increase the risk of HCC, decompensation and death/transplant, respectively. Those identified by more than one study include alpha-fetoprotein (6, 7, 13, 20), male sex (6, 7, 20, 22) and lack of IFN treatment (13-15, 21) as independent risk factors for HCC; albumin (6, 8, 13, 18) and total bilirubin (7, 13, 20) as independent risk factors for decompensation; and platelets (8, 11, 16, 22), albumin (6, 8, 16, 18, 20-22), increasing age (7, 8, 11, 15, 16, 22) and presence of oesophageal varices (7, 22) as independent risk factors for death/transplantation.

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Discussion

Here we present a summary of the data from thirteen studies published during the last fourteen years on the outcome of compensated HCV cirrhosis. These data indicate that the estimated annual rate of developing any complication of HCV cirrhosis (including an episode of decompensation or development of HCC) is 6.37%; of developing HCC is 3.36% per annum, and of death/transplant is 4.58% per annum. Although the total number of patients included in the analysis is large (2386), heterogeneity in reporting reduced the number of patients where the impact of chronic HCV infection could be distinguished from other causes of cirrhosis.

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Variability in patient characteristics may account for some of the differences seen between the studies. Gender distribution was markedly different and this may have influenced outcomes as male gender is thought to be a risk factor for disease progression in HCV (4). In keeping with this, the study with the greatest proportion of male participants also showed one of the highest annual rates of death/transplant (21). The average age of participants in most studies did not vary greatly, but there were two notable outliers and it is of interest that the study that reported the highest rate of complications (11.7% per annum (6)) was also the study with the oldest average age of participants, and that the study with the youngest average age (18) was among the lowest (4.76% per annum). Whilst Far Eastern origin has been suggested as a risk factor for progression in HCV cirrhosis, particularly with regard to HCC development (16), the mean annual percentage rates of death/transplantation and HCC development reported by the Japanese studies were not significantly higher than those reported by the most comparable Western European studies included in this analysis. The publication dates of studies included here span 13 years (1996 – 2009). However the recruitment periods of these studies (1982 – 2007) overlap by a considerable degree, therefore further analysis of the results according the date of the study was not pursued.

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Two studies included patients who were HCV RNA negative (17, 21) although the proportion of such patients was small. These patients may have had ongoing HCV infection with RNA levels below the lower limit of detection of the study laboratory, or alternatively it is possible that these patients had an

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alternative cause for cirrhosis. Sangiovanni *et al* (20) excluded HCV antibody-positive, RNA-negative patients from their analysis, but acknowledged that the small number of such patients meant it was not possible to assess whether their course of disease was significantly different from that of patients who were RNA seropositive.

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Three studies (16, 17, 20) presented combined outcome data from patients with cirrhosis due to HCV infection alone, and from patients with HCV infection plus additional causes for chronic liver disease (including HBV coinfection, alcohol abuse and hereditary haemochromatosis). HCV RNA seropositivity was confirmed in all patients considered HCV infected in two of these studies (16, 20) although in only 89% of those considered to have HCV infection in the third study (17). Separate analysis showed shortened survival amongst those with HCV and coexistent causes of liver disease, (16, 20) and the incidence of HCC appears increased in HCV/HBV coinfected patients, compared to patients with HCV cirrhosis alone (17). Although the numbers of such patients included in the overall outcome data were relatively small, it is possible that their inclusion may have increased the observed complication rates.

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Whilst these studies recognised alcohol abuse (>80g/day) as a contributor to disease progression in a proportion of patients, alcohol consumption at lower levels was not an exclusion criterion in any study, and may have been an unrecognised cofactor in the progression of cirrhosis. Self-reporting of alcohol intake amongst participants may have underestimated total intake (23). The interactions between alcohol and HCV in chronic liver disease are incompletely understood, but appear to involve earlier onset and more rapidly progressive fibrosis even with levels of alcohol consumption as low as 20g/day, and a synergistic effect of HCV and alcohol on HCC development at higher levels of consumption (>80g/day) (reviewed in (24)). The effect of alcohol consumption on disease progression in these HCV infected cohorts may therefore have been significant. Similarly, metabolic syndrome,

thought to be another cofactor in progression of HCV cirrhosis (25), is not featured or controlled for in patient selection in these studies.

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The effect of IFN treatment on disease progression in HCV cirrhosis remains controversial, with previous studies variously showing no effect of IFN on outcomes in HCV cirrhosis (26), a reduction in rates of HCC (14, 27, 28), or prevention of disease progression (29) with improved survival (30). Differences in results seen have been attributed to variations in patient selection, IFN treatment doses and regimens, and bias associated with retrospective cohort studies (13). Due to the clear benefits of interferon and ribavirin-based treatment regimens for HCV, ethical considerations have limited the ability to conduct randomised controlled trials in this area. The present analysis included a non-randomised controlled trial evaluating the effect of IFN on HCV cirrhosis, which found no effect on overall or event free survival, although there did seem to be a beneficial effect of IFN therapy on development of HCC (13). An independent protective effect of IFN therapy on HCC development and rates of decompensation in HCV cirrhosis has been demonstrated at multivariate analysis by some (14, 15, 18, 20), but not all (8), of the other studies included in this analysis. Bruno *et al* found a beneficial effect of interferon therapy on rate of decompensation and liver-related mortality, but only in those who achieved a sustained virological response (7).

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In an attempt to establish whether the inclusion of patients who had undergone antiviral therapy in some studies had influenced the reported mean annual percentage rates for death/transplantion, decompensation or HCC, these outcomes were compared between studies in which some participants had received therapy versus those in which all participants were untreated. The difference was significant only for occurrence of HCC, with a higher mean annual rate of HCC reported by studies in which no participants received antiviral therapy. Whilst the inclusion of outcomes for patients who had received IFN may have led to an underestimation of HCC rates in chronic HCV cirrhosis, it is also possible that selection bias may have led to an overestimation of complication rates in the studies

reporting outcomes exclusively in untreated patients. The untreated patients whose outcomes were reported by Bruno *et al* were older, had higher Model for End Stage Liver Disease (MELD) scores and were more likely to have oesophageal varices than the patients from this study who received treatment (7). However, other reports emphasize that interferon therapy was withheld on the basis of patient choice (14, 15), concomitant non-liver disease (14), or withheld from matched patients as part of a controlled trial (13). Unfortunately, the studies which reported outcomes for treated patients did not elaborate on the reasons for providing or withholding anti-viral treatment. Therefore it is difficult to predict how the comparison of treated versus untreated may be skewed.

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In view of recent reports indicating that maintenance therapy with low dose pegylated IFN does not reduce the incidence of complications of chronic HCV in those who do not eradicate the virus (30), the value of viral eradication in patients with cirrhosis remains to be determined and further studies should address this important issue. Similarly it will be important to ensure that future studies clearly differentiate between treatment responders and failures. It is to be hoped that the heterogeneity of reporting that we have documented will lead to better descriptions of the patient populations in future studies of the outcome of cirrhosis.

A number of independent variables have been postulated as independent markers for development of complications of cirrhosis, and whilst further analysis was not possible here, the variables identified most frequently are in accord with scoring systems used internationally to evaluate severity of liver disease (such as MELD). Furthermore, two studies evaluated the significance of oesophageal varices and both found their presence to be independently associated with death in compensated HCV cirrhosis (7, 22).

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Overall, the summary data presented here provide estimated rates of progression of compensated HCV cirrhosis derived from patient groups comprising treated and untreated patients, from a range of geographic locations and with varied alcohol consumption. These data confirm the relatively slow

progress of HCV cirrhosis. However, they highlight the need for increased vigilance for development of HCC, particularly in those with cofactors for progressive liver disease.

Acknowledgements

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Conflict of interests

Professor Foster has performed consultancy work, received grants from and spoken on behalf of companies (including Roche, Novartis, Human Genome Science, Tibotec, GSK and Chughai) who market and/or are developing drugs to treat chronic Hepatitis C.

Study	Country	Study design	Number of HCV (+) participants	Duration (yrs)	Outcomes assessed				
					Death	Transplant	HCC	Decompensation	Increased CP score
Gramenzi *et al*, 2001 (13)	Italy	Non-random controlled	72	4.8	✓	✓	✓	✓	
Mazzella *et al*, 1996 (14)	Italy	Prospective cohort	92	2.8			✓		
Okanoue *et al*, 1999 (12)	Japan	Retrospective cohort	55	5.6			✓		
Shiratori *et al*, 2005 (15)	Japan	Prospective cohort	74	6.8	✓		✓		
Kobayashi *et al*, 2006 (16)	Japan	Prospective cohort	490	8.2	✓		✓	✓	
Sangiovanni *et al*, 2006 (20)	Italy	Prospective cohort	214	9.5	✓	✓	✓	✓	✓
Benvegnu *et al*, 2004 (17)	Italy	Prospective cohort	312	7.6	✓	✓	✓	✓	✓
Hu *et al*, 1999 (18)	USA	Prospective cohort	112	4.5	✓	✓	✓	✓	
Serfaty *et al*, 1998 (21)	France	Prospective cohort	103	3.3	✓	✓	✓	✓	
Fattovich *et al*, 2002 (8)	Western Europe	Retrospective cohort	136	6.8	✓	✓	✓	✓	
Toshikuni *et al*, 2009 [6]	Japan	Prospective cohort	152	5.4	✓		✓	✓	
Degos *et al*, 2000 (22)	France	Prospective cohort	416	5.6	✓		✓		
Bruno *et al*, 2009 (7)	Italy	Prospective cohort	158	14.4	✓	✓	✓	✓	

Table 1. Characteristics of eligible studies identified for inclusion. HCV, hepatitis C virus; HCC, hepatocellular carcinoma; CP, Child-Pugh. Duration is given as median years, with the exception of Mazzella *et al* (14), Okanoue *et al* (12) and Hu *et al* (18), where it is given as mean years.

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Study	Inclusion Criteria				Exclusion Criteria							
	HCV (+)	Biopsy proven cirrhosis (n (%))	Alcohol (max g/day)	Abnormal ALT / AST	HCC	HIV	Other Liver Disease	Ascites	PSE	Variceal Bleeding	Jaundice	Use of Diuretics
Gramenzi *et al*, 2001 (13)	✓	48 (67)	60	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mazzella *et al*, 1996 (14)	✓	92 (100)										
Okanoue *et al*, 1999 (12)	✓	55 (100)	60		✓		✓	✓			✓	
Shiratori *et al*, 2005 (15)	✓	74 (100)			✓		✓					
Kobayashi *et al*, 2006 (16)	✓	490 (100)			✓	✓	✓	✓	✓	✓		
Sangiovanni *et al*, 2006 (20)	✓	214 (100)			✓			✓		✓	✓	✓
Benvegnu *et al*, 2004 (17)	✓	Not given			✓			✓	✓	✓	✓	
Hu *et al*, 1999 (18)	✓	106 (94.5)	80		✓	✓	✓	✓	✓	✓	✓	
Serfaty *et al*, 1998 (21)	✓	103 (100)	80	✓	✓	✓	✓	✓	✓	✓	✓	
Fattovich *et al*, 2002 (8)	✓	136 (100)	80		✓		✓	✓	✓	✓	✓	
Toshikuni *et al*, 2009 (6)	✓	Not given			✓		✓					
Degos *et al*, 2000 (22)	✓	416 (100)			✓	✓	✓					
Bruno *et al*, 2009 (7)	✓	Not given			✓	✓	✓	✓	✓	✓		

Table 2. Inclusion and exclusion criteria utilised by eligible studies. The proportion of patients where cirrhosis was diagnosed by liver biopsy was not given by Toshikuni *et al* (6), and was given for all patients but not for the subgroup of HCV monoinfected, untreated patients whose outcomes were considered in this analysis by Benvegnu *et al* (17) and Bruno *et al* (7). HCV, hepatitis C virus, AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; PSE, porto-systemic encephalopathy.

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Study	Gramenzi *et al*, 2001 (13)	Mazzella *et al*, 1996 (14)	Okanoue *et al*, 1999 (12)	Shiratori *et al*, 2005 (15)	Kobayashi *et al*, 2006 (16)	Sangiovanni *et al*, 2006 (20)	Benvegnu *et al*, 2004 (17)	Hu *et al*, 1999 (18)	Serfaty *et al*, 1998 (21)	Fattovich *et al*, 2002 (8)	Toshikuni *et al*, 2009 (6)	Degos *et al*, 2000 (22)	Bruno *et al*, 2009 (7)
Age (years)	58.1 (7.8)	54 (1.22)	57.6 (5.2)	61 (no range)	59 (25-82)	55 (7)	61 (36-78)	52.1 (no range)	56 (14)	58 (22-79)	69 (35-83)	57 (46-64)	Not given
Males (n (%))	33 (46)	52 (57)	28 (51)	35 (47)	289 (59)	106 (50)	142 (56)	56 (50)	33 (75)	81 (60)	57(38)	240 (58)	74 (46.8)
HCV diagnosis: Antibody + (n(%))	72 (100)	92 (100)	55 (100)		490 (100)	214 (100)	254 (100)		103 (100)	136 (100)	152 (100)	416 (100)	158 (100)
RNA + (n (%))			55 (100)	74 (100)	490 (100)	214 (100)	225 (89)	112 (100)	97 (94)		152 (100)		158 (100)
Bilirubin (mg/dl)	1.1 (0.5)	0.92 (0.04)			1.1 (0.4-3.0)		0.81 (0.12-2.57)	0.9 (0.6)	0.99 (0.53)		0.9 (0.3 – 2.0)	0.88 (0.64 –1.23)	0.9 (0.7 – 1.1)
ALT (IU/l)	89 (64)	148 (11.2)	118 (38)	75 (no range)	58 (9-315)		130 (18-973)	139.6 (111.6)	96 (68)		48 (12 – 230)		
Platelets (x1000mm^3)	140.3 (74)		97 (25)	105 (no range)	96 (17-398)		131 (31-294)	171.6 (71.9)	124 (49)		103 (21 – 277)	123 (88-170)	117 (100-155)
Albumin (g/dl)	3.8 (0.5)	4.0 (0.03)		4.0 (no range)	3.8 (3.0-5.1)		4.2 (3.2-5.3)	4.1 (0.4)	3.9 (0.5)		3.8 (3.0 – 4.8)	4.1 (3.8 – 4.5)	4.2 (3.9-4.5)
Treated (n (%))	0	0	0	0	0	23 (11)	115(45)	49 (44)	59 (57)	0	0	223 (54)	0

Table 3. Baseline characteristics of participants. Where not otherwise specified, figures are given as mean (SD) or median (range), depending on the measure used by the source study. Descriptive data given are for the untreated (control arm) of the trial reported by Gramenzi *et al* (13) and for patients who did not receive treatment in the studies by Mazzella *et al* (14), Okanoue *et al* (12), Shiratori *et al* (15), Serfaty *et al* (21) and Bruno *et al* (7). The data is for HCV monoinfected patients in the studies reported by Kobayashi *et al* (16), Benvegnu *et al* (17) and Fattovich *et al* (8), for patients without additional/alternative liver disease reported by Sangiovanni *et al* (20) and Toshikuni *et al* (6), and for all participants reported by Hu *et al* (18) and Degos *et al* (22). "Treated" refers to the number of study participants included in the outcomes analysis who received treatment during the follow up period. HCV, Hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutaryltransferase; AFP, alphafetoprotein; s, seconds.

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Study	Gramenzi *et al*, 2001 (13)	Mazzella *et al*, 1996 (14)	Okanoue *et al*, 1999 (12)	Shiratori *et al*, 2005 (15)	Kobayashi *et al*, 2006 (16)	Sangio-vanni *et al*, 2006 (20)	Benvegnu *et al*, 2004 (17)	Hu *et al*, 1999 (18)	Serfaty *et al*, 1998 (21)	Fattovich *et al*, 2002 (8)	Toshikuni *et al*, 2009 (6)	Degos *et al*, 2000 (22)	Bruno *et al*, 2009
N	72	92	55	74	490	214	312	112	103	136	152	416	
Average follow-up (years)	4.8	2.8	5.6	6.8	8.2	9.5	7.6	4.5	3.3	6.8	5.4	5.6	
Lost to follow up (n (%))	3 (4)			16 (22)		66 (31)	35 (14)		3 (3)	15 (11)	87 (57)		
Death, transplant (n (%));	11 (15)			24 (44)	270 (55)	75 (35)	*(N=312)* 65 (21)	22 (20)	19 (18)	35 (26)	44 (29)	83 (20)	
Liver failure	7 (10)			8 (33)	25 (9)	15 (7)	15 (5)	14 (13)	5 (5)	18 (13)	15 (10)		
Varices	2 (3)				6 (1)	6 (3)	2 (1)		1 (1)		3 (2)		
HCC	1 (1)			11 (46)	200 (41)	33 (15)	41 (13)	7 (6)	9 (9)	17 (13)	17 (11)		
Sepsis					17 (4)						3 (2)		
Non liver	1 (1)			5 (21)	22 (5)	20 (9)	13 (4)	1 (1)	1 (1)	17 (13)	6 (4)		
Complications:	32 (44)						*(N = 254)* 78 (31)	24 (21)	26 (25)	72 (53)	96 (63)		63 (40)
HCC	19 (26)	9 (10)	22 (40)	35 (47)		68 (32)	52 (21)	9 (8)	11 (11)	23 (17)	46 (30)	60 (14)	53 (34)
Ascites	11 (15)					50 (23)	45 (18)	10 (9)			32 (21)		
GI bleed	1 (1)					13 (6)	12 (5)	5 (5)			2 (1)		
PSE	1 (1)					2 (1)	5 (2)	4 (4)			9 (6)		
Jaundice						36 (17)		9 (8)			7 (5)		

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Table 4. Outcomes for participants in each eligible study, where the data were provided. N refers to the number of study participants for whom this data has been grouped, and may include some treated patients or patients with additional liver disease (discussed further in the text). Outcome data is given as number of participants (percentage of N). PSE, portosystemic encephalopathy; HCC, hepatocellular carcinoma.

Study	Gramenzi *et al*, 2001 (13)	Mazzella *et al*, 1996 (14)	Okanoue *et al*, 1999 (12)	Shiratori *et al*, 2005 (15)	Kobayashi *et al*, 2006 (16)	Sangio - vanni *et al*, 2006 (20)	Benvegnu *et al*, 2004 (17)	Hu *et al*, 1999 (18)	Serfaty *et al*, 1998 (21)	Fattovich *et al*, 2002 (8)	Toshikuni *et al*, 2009 (6)	Degos *et al*, 2000 (22)	Bruno *et al*, 2009 (7)	**Weighted Mean ***
Death/transplant: (%)	3.18			4.77	6.72	3.69	2.74	4.37	5.59	3.78	5.36	3.52	3.91	**4.58**
Liver failure	2.03			1.59	0.62	0.74	0.63	2.78	1.47	1.95	1.83			**1.16**
Varices	0.58				0.15	0.30	0.08		0.29		0.36			**0.22**
HCC	0.29			2.19	4.98	1.62	1.73	1.39	2.65	1.84	2.07			**2.70**
Sepsis					0.42						0.36			**0.41**
Non-liver	0.29			0.99	0.55	0.98	0.55	0.20	0.29	1.84	0.73			**0.70**
Complications: (%)	9.26						4.04	4.76	7.65	7.79	11.70		2.77	**6.37**
HCC	5.50	3.49	7.14	6.96		3.34	2.69	1.79	3.24	2.49	5.60	2.54	2.33	**3.36**
Ascites	3.18					2.46	2.33	1.98			3.90			**2.69**
Variceal bleed	0.29					0.64	0.62	0.99			0.24			**0.58**
PSE	0.29					0.10	0.26	0.79			1.10			**0.45**
Jaundice						1.77		1.79			0.85			**1.48**

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Table 5. Outcome data calculated as annual percentage rates, derived from the raw data provided by each study. HCC, hepatocellular carcinoma; PSE, porto-systemic encephalopathy.

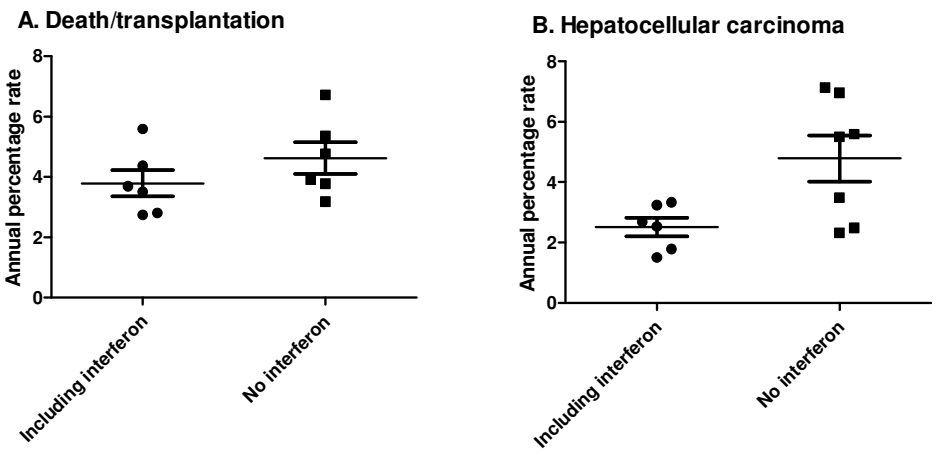

Figure 1. Annual percentage rates for outcomes according to inclusion of patients who had received interferon in the reported results. A: Mean annual percentage rates of death/transplant were 3.79 ± 0.44 and 4.62 ± 0.52 in studies reporting outcomes where some patients received interferon and those which did not include interferon treated patients in outcomes, respectively (mean ± SEM, $P = 0.25$). B: Mean annual percentage rates of hepatocellular carcinoma were 2.52 ± 0.34 and 4.79 ± 0.76 in studies reporting outcomes where some patients received interferon and those which did not include interferon treated patients in outcomes, respectively (mean ± SEM, $P = 0.02$).

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Section/topic	#	Checklist item	Repo on pa
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
wRationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3, 13
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3-4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3-4

Section/topic	#	Checklist item	Repo on pa

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3-4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4-5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	4-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	4-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4-9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	4-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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