Excess mortality rates in a cohort of patients infected with the hepatitis C virus: a prospective study

Keith R Neal, on behalf of the Trent Hepatitis C Study Group*

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Objective: We analysed the Trent Hepatitis C cohort to determine standardised mortality ratios in patients infected with hepatitis C virus (HCV), and to identify risk factors and associations with all-cause and liver-related mortality.

Design: Cohort study.

Setting: Patients with HCV infection attending secondary care within the Trent region of England.

Patients: 2285 patients with hepatitis C, followed for 1 year or more.

Main outcome measures: The death rate in the cohort was compared to that seen in an age- and sex-matched English population. We performed Cox regression analyses to identify factors predictive of all-cause mortality and deaths from liver disease.

Results: Standardised mortality ratios in the cohort were three times higher than those expected in the general population of England. The excess deaths were due to liver-related causes and those associated with a drug-using lifestyle. Significant independent predictors of all-cause mortality were age, sex, treatment (protective) and liver biopsy fibrosis. Age, treatment, liver biopsy fibrosis and mean alcohol consumption were predictors of liver-related mortality. HCV was mentioned on 23% of death certificates overall, and on 52% of those of patients dying from a liver-related cause.

Conclusions: Our findings demonstrate that the death rate in patients infected with hepatitis C is three times higher than expected. Severity of disease is associated with a worse prognosis, whilst treatment improves outcome, particularly in those who respond. Use of death certificate data on HCV infection for planning purposes will result in considerable under-estimation of the HCV-related disease burden.

Correspondence to:
Professor W L Irving,
Department of Microbiology,
University Hospital, Queen's
Medical Centre, Nottingham
NG7 2UH, UK; will.irving@
nottingham.ac.uk

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Hepatitis C virus (HCV) is a major cause of chronic liver disease worldwide.¹ The potential impact of HCV on health service resources has been recognised by the implementation of hepatitis C strategies by the Departments of Health of the four governments of the United Kingdom.² Although the natural history of HCV infection has been clarified by recent studies,^{3–5} key questions about the long-term disease burden and benefits of treatment remain unanswered. In particular, data on the morbidity and mortality associated with HCV infection is of major importance to the development of rational national strategies. This issue has so far been studied only in selected population subgroups, such as those who acquired infection through blood transfusion⁶ or contaminated intravenous immunoglobulin preparations,^{7,8} or in military recruits.⁹ Some of these cohorts, particularly young women infected by anti-D immunoglobulin,^{7,8} appear to have a good prognosis. There is, however, a need to understand the morbidity and mortality of HCV infection in cohorts more representative of the other infected populations.

The Trent Hepatitis C Cohort Study was established in 1992 with the aim of elucidating the natural history of HCV by the prospective study of an unselected, population-based cohort of infected individuals in the Trent region of England.¹⁰ In this report, we describe the all cause and liver-related mortality in the Trent HCV cohort.

METHODS

The Trent HCV cohort

Details of the Trent Hepatitis C cohort have been described elsewhere.¹⁰ Briefly, patients who attend one of the study centres are asked to consent to inclusion. Data on demography, risk factors for infection, dates of exposure to risk, laboratory investigations, biopsies and treatments are stored in a linked

anonymised database. HCV-infected patients with haemophilia or HIV co-infection and those who were identified through screening on renal dialysis units are identifiable within the database but excluded from further analysis, as the natural history of disease may differ in these groups. Ethics approval for the Trent HCV cohort and associated studies was obtained from the Yorkshire Multicentre Research Ethics Committee.

Most participants within the Trent cohort are registered with the National Health Service Central Register (NHSCR).¹¹ This system covers nearly all residents of England and Wales and has reciprocal links to the equivalent Scottish register. It identifies deaths, cancer registrations and emigrations and forwards this information monthly to the study group. When a death is identified by the NHSCR, a copy of the death registration data, including the coroner's findings where available, is forwarded to the responsible clinician (KRN). Deaths are also reported to KRN from the individual participating clinics. Using this information, the underlying causes of death were categorised according to the criteria shown in table 1. Deaths within the first year of diagnosis of HCV infection were excluded to reduce selection bias.

Data extracted

Length of survival during follow-up within the cohort was calculated by using the earliest known positive HCV test result and the later of (i) date of death or (ii) date the patient was last seen at a participating hospital. For those patients last seen before 31 December 2005, and who were registered with the NHSCR, the date of 31 December 2005 was used, as this

Abbreviations: HCC, hepatocellular cancer; HCV, hepatitis C virus; NHSCR, National Health Service Central Register; SMR, standardised mortality ratio

Table 1 Categorisation of causes of death

Category	Details
Liver	Any condition related to liver pathology and complications thereof. Includes deaths where alcohol was the only mentioned aetiology of liver disease Also includes deaths related to systemic infections where liver disease or post-transplant immunosuppressive treatment was a major factor
Hepatocellular cancer	Hepatocellular cancer and complications of treatment
Unrelated medical	Includes deaths from causes such as coronary heart disease, strokes, cancers unrelated to HCV, road traffic accidents and maternal deaths
Drug related	Recreational and illegal drug use. Accidental overdoses. Sepsis and inhalational pneumonia in a known injector. As reported by the coroner
Suicide	As reported by the coroner
Murder	As reported by the coroner

allowed sufficient time for the death to be notified by the NHSCR by 30 June 2006. Patients dying within the first year of follow-up within the cohort were excluded from the analyses.

Data were extracted from the database, where available, on date of birth, sex, ethnicity, risk factors for HCV infection, alcohol consumption, ALT results (IU/ml), HCV RNA status, HCV genotype, past and current hepatitis B infection (by anti-HBc and HBsAg testing, respectively), liver fibrosis stage, treatment for HCV and response to treatment. Ethnicity was defined using the major categories used in the English census of 2001.¹² Risk factors for HCV infection were categorised hierarchically as injecting drug use, in non-drug users receipt of blood/blood product transfusion before 1991/1985 respectively, other risk factors (non-professional tattoo, unprotected intercourse with known HCV-infected partner, being born abroad) in non-drug users without a history of transfusion, none of the above, or data missing. Alcohol consumption was recorded in two ways: "ever heavy drinking" was defined as intake of 50 or more units of alcohol per week for a minimum period of 6 months; mean alcohol consumption was the average number of alcohol units drunk weekly as recorded at the clinic visits after diagnosis. HCV RNA status was determined using a commercially available genome amplification technique (Amplicor, Roche Diagnostics, Basel, Switzerland), which detects down to 50 IU/ml. Patients were classified as being "ever positive" or "always negative". Liver fibrosis was assessed by the Ishak scoring of liver biopsy histology.¹³ For some variables two or more results were available. Where there was more than one biopsy the highest Ishak fibrosis score was used. For therapies, the most recent treatment given and the best response to treatment were used.

Table 2 Decade of birth and gender of patients included

Decade of birth	Male	Female	Total
Before 1920	9	2	11
1920–29	34	19	53
1930–39	33	34	67
1940–49	100	57	157
1950–59	446	204	650
1960–69	530	228	758
1970–79	327	183	510
1980 onwards	40	39	79
Total	1519	766	2285
Mean duration of follow-up (years)	6.7	7.1	6.8

Statistical methods

Standardised mortality ratios

The all-cause sex-specific death rates and life expectancies for the general population of England by individual year of age were obtained from the Office for National Statistics and the Department of Health for the periods from 1991 to 2004.¹⁴ Hence, the population of England was used as control comparator group.

For each calendar year that a patient was part of the cohort, age and sex were determined and the appropriate age- and sex-specific death rates were used to calculate the individual mortality risk for each member of the cohort. These total mortality risks were added together to obtain the expected number of deaths in the cohort if the average death rates in

Figure 1 Category of death by age at death.**Table 3** Distribution of causes of death, age at death and presence of HCV on death certificate by category

Category of death	Mean age at death (SD)	Mean duration of follow-up (SD)	Male	Female	Total	HCV mentioned on certificate	Chronic alcohol use
Drug related	36.0 (7.7)	4.4 (2.4)	24	8	32	0	0
Hepatocellular cancer	63.7 (12.5)	6.2 (3.1)	14	8	22	8 (36%)	0
Liver*	51.4 (10.9)	4.9 (2.8)	38	14	52	26 (50%)	11† (24%)
Murder	42.0 (7.1)	5.3 (0.3)	2	0	2	0	0
Suicide	36.0 (7.7)	6.4 (4.1)	6	1	7	0	0
Unrelated medical	58.7 (16.4)	5.7 (3.4)	41	10	51	8 (16%)	0
Cause unascertained	51.8 (17.7)	7.1 (3.6)	11	3	14	NA	NA
Total	51.6 (16.0)	5.6 (3.1)	136	44	180	42 (23%)	

*Includes alcoholic liver disease and alcoholism but does not include the mention of alcohol in association with overdoses; †in eight patients, both HCV and alcohol were mentioned on the death certificate.

Table 4 Standardised mortality ratios for males and females

Gender	Known deaths	Expected deaths	Standardised mortality ratio (95% CI)	Average years of life lost per death	Non-standardised annual death rate/1000 (95% CI)
Males	136	45.8	3.0 (2.3 to 4.2)	26.7	13.36 (10.7 to 16.0)
Females	44	14.6	3.0 (2.0 to 6.3)	27.0	8.09 (5.1 to 11.1)

England had applied to the whole cohort. Standardised mortality ratios (SMRs) were calculated by dividing the cohort deaths by the expected number of deaths as calculated above. The 95% confidence intervals were calculated using the Poisson distribution.

Risk factors for death

Survival analyses were carried out for all-cause mortality and liver-related mortality. Cox proportional hazards survival analyses were calculated using SPSS V13.0 (SPSS, Chicago, IL). All variables were included in at least one multivariate

Table 5 Hazard ratios for individual risk factors for all-cause mortality, controlled for age and sex, in a cohort of 2285 patients

Factor	Died, n	Alive, n	Hazard ratio (95% CI)	p Value
Age at diagnosis (n = 2285)				
Per year	–	–	1.06 (1.05 to 1.07)	<0.001
Sex (n = 2285)				
Male	136	1383	1.7 (1.2 to 2.4)	0.02
Female	44	722		
Ethnicity (n = 2131)				
White	149	1822	Ref	0.1
Mixed	1	5	3.6 (0.5 to 26)	
Indian subcontinent	12	87	1.6 (0.8 to 2.9)	
African/Caribbean	7	40	0.5 (0.2 to 1.1)	
Other	0	8	0 (0 to inf)	
Injecting drug use (n = 2108)				
Yes	89	1469	0.9 (0.6 to 1.3)	0.5
No	71	479		
Ever heavy drinker (n = 1737)				
Yes	68	815	1.8 (1.2 to 2.6)	0.008
No	45	809		
Current alcohol consumption (n = 1835)				
Per weekly unit	–	–	1.003 (0.998 to 1.008)	0.3
Mean ALT (n = 2083)				
Per unit	–	–	1.001 (1.0 to 1.002)	0.003
PCR (n = 2265)				
Positive	157	1784	1.1 (0.7 to 1.8)	0.7
Negative	21	303		
Genotype (n = 1694)				
PCR negative	21	303	Ref	0.02
1	40	571	0.9 (0.5 to 1.5)	
2	8	108	0.7 (0.3 to 1.7)	
3	39	562	0.9 (0.6 to 1.6)	
4	2	27	1.0 (0.2 to 4.4)	
5	6	7	4.3 (1.7 to 10.9)	
Hepatitis B (n = 1699)				
Any marker	51	565	0.9 (0.6 to 1.3)	0.6
Never infected	71	1012		
Worst Ishak fibrosis score (n = 2285)				
0	16	384	Ref	<0.001
1	16	326	1.0 (0.5 to 2.1)	
2	2	155	0.2 (0.1 to 1.1)	
3	9	132	1.0 (0.5 to 2.4)	
4	3	53	0.6 (0.1 to 1.9)	
5	15	83	2.1 (1.1 to 4.3)	
6	48	106	4.3 (2.4 to 7.7)	
No biopsy	71	866	1.9 (1.1 to 3.2)	
Any treatment (n = 2285)				
Yes	57	776	0.6 (0.5 to 0.9)	0.004
No	123	1329	Ref	
Started treatment (n = 2285)				
Ribavirin+PEG-IFN	19	549	0.3 (0.2 to 0.6)	<0.001
IFN+ribavirin	12	122	0.9 (0.5 to 1.6)	
IFN	26	105	1.2 (0.8 to 1.8)	
None	123	1329	Ref	
Response to treatment* (n = 681)				
Non-responder or withdrawn	39	195	Ref	<0.001
Sustained responder	8	343	0.1 (0.06 to 0.3)	
Relapsed after response	4	95	0.2 (0.09 to 0.7)	

*Does not include the 152 people without post-treatment follow-up.

Table 6 Multivariate analysis for all-cause mortality

	Hazard ratios (95% CI)	p Value
Gender		
Male	1.82 (1.3 to 2.6)	0.001
Female	Ref	
Age		
Per year	1.048 (1.04 to 1.06)	<0.001
Treatment		
Ribavirin+PEG-IFN	0.25 (0.1 to 0.4)	<0.001
IFN+ribavirin	0.60 (0.3 to 1.1)	
IFN	0.75 (0.5 to 1.2)	
None	Ref	
Most severe Ishak fibrosis score		
0	Ref	<0.001
1	1.23 (0.6 to 2.5)	
2	0.36 (0.1 to 1.6)	
3	1.67 (0.7 to 3.8)	
4	1.24 (0.3 to 4.5)	
5	4.14 (1.9 to 8.9)	
6	6.33 (3.4 to 11.7)	
No biopsy	1.76 (1.02 to 3.0)	

model. Tests for proportionality were performed using log minus log plots (all models satisfied this condition). Liver-related mortality included liver disease, deaths from liver-related causes and hepatocellular cancer (HCC).

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

The study cohort comprises 2285 patients with HCV infection of whom 1809 have been registered with the NHSCR, together with 476 other patients who were not registered but who have been followed for at least 1 year. The demography of the cohort is shown in table 2. Mean follow-up for the study group was 6.7 years, inter-quartile range 3.6–9.1 years. A total of 442 patients have been followed for more than 10 years (19%).

There were 180 deaths eligible for inclusion in this study. A further 26 cohort patients died during the first year of follow-up and were excluded. Eleven of those were from liver-related causes. Figure 1 shows overall deaths by cause segregated for each age decile. The causes of death categorised by gender and mean ages of death are shown in table 3. This table also includes information on whether HCV or chronic alcohol use was specifically recorded on the death certificate. The SMRs, years of life lost, and non-age-standardised death rates for all causes of death for males and females are shown in table 4.

In order to assess the predictors of all-cause and liver-related death, hazard ratios for individual risk factors for all-cause mortality, controlled for age and sex, were deduced. These are shown in table 5 and identify a number of potential predictors of mortality.

In a multivariate model, however, gender, age, fibrosis stage and a history of having received treatment for HCV were identified as the only predictors of all-cause mortality (table 6).

Table 7 illustrates the univariate analysis for liver-related mortality (comprising the 74 liver and HCC deaths from table 3) and table 8 shows the multivariate model, in which the fibrosis categories have been reduced to eliminate zero terms.

Table 8 demonstrates that gender is not a predictor of liver-related mortality, but that age, Ishak fibrosis score and a history of treatment are again highly significant predictors of outcome.

Table 9 shows the outcome of the 350 treatment-naïve patients who were subsequently treated with pegylated interferon and ribavirin and who were scheduled to complete therapy before 30 September 2005, thus allowing virological outcome at 6 months post treatment to be determined for all patients.

DISCUSSION

The Trent HCV cohort is a representative cohort of HCV-infected individuals in the UK,^{10 15} with patients recruited from the majority of secondary care centres in the East Midlands, South Yorkshire and Leeds. Referrals of patients from outside the catchment areas to specialist centres were specifically excluded. The cohort therefore reflects the population seen in secondary care across the region. The relatively young age of the cohort compared to the general population is consistent with the known epidemic curve of HCV infection since the 1960s.¹⁶

The principal finding of this study is that HCV-infected persons have a death rate three times higher than that of the general population. Excess mortality is due to significant numbers of deaths from both injecting drug use and liver disease. The 12-year age difference in deaths from liver disease compared with those from HCC is consistent with the known natural progression of hepatitis C disease.¹ There were 58 deaths from unrelated medical causes and suicide (excluding unascertained), very close to the 60 deaths from all causes that would have been expected in this cohort (table 4). Of particular note is the low age at death, which was 51.6 years on average. This is largely a result of lifestyle-related causes including the illicit use of drugs, murder and suicide, all of which are relatively rare in the general population.

A community-based study¹⁷ from Australia on mortality in HCV patients using very different methodology (linking notified patients with death registrations) also showed a death rate three times higher with HCV infection and that this excess was split equally between drug-related deaths and liver deaths. The population of New South Wales and the behaviour of those most at risk of HCV infection is likely to be very similar to that in the Trent region.

The causes of death are missing for 14 patients, either because of very recent death or because the patients were lost to follow-up before they were registered with NHSCR and so had not consented. These deaths were determined from the notes or hospital patient information systems, but cause of death was not recorded. These patients had the same age and sex distribution as those for whom we have a known cause, and therefore the distribution of causes of death in this group is likely to be similar. This will have had the effect of underestimating the true incidence of liver and drug-related death. Further, many patients with HCV are unaware they are infected, and a high proportion of patients known to be infected are not referred to secondary care.¹⁸ Patients who have acquired HCV infection from injecting drug use are now the main source of new referrals, reflecting the elimination of blood transfusion and poor medical practice as a route of transmission in the UK and other developed countries.^{1 16} These drug users are usually referred by drug and alcohol services and we note that attenders at these services are known to survive longer than those who are referred but who do not attend.¹⁹ The real risk to the whole HCV-infected population is therefore likely to be even higher than that evident in our cohort. Our survival analyses did not show an association with injecting drug use after controlling for age. However, a majority of the cohort are drug users which mitigates against demonstrating an “exposure” effect when so many are exposed. Also, there is a major age discrepancy between drug users

Table 7 Hazard ratios for individual risk factors for liver-related mortality, controlled for age and sex in a cohort of 2271 patients*

Factor	Died	Alive and non-liver-related death	Hazard ratio (95% CI)	p Value
Age at diagnosis (n = 2271)			1.069 (1.06 to 1.08)	<0.001
Sex (n = 2271)				
Male	52	1456	1.32 (0.8 to 2.17)	0.2
Female	22	741	Ref	
Ethnicity (n = 2118)				
White	63	1897	Ref	0.3
Mixed	0	6	0 (0)	
Indian subcontinent	5	92	1.55 (0.5 to 3.5)	
African/Caribbean	3	44	0.3 (0.1 to 1.0)	
Other	0	8	0 (0)	
Risk factor (n = 2098)				
Intravenous drug abuse	30	1522	0.71 (0.4 to 1.3)	0.2
Other	36	510	Ref	
Ever heavy drinker (n = 1727)				
Yes	30	847	2.12 (1.1 to 4.0)	0.02
No	20	830	Ref	
Current alcohol consumption (n = 1826)				
Per weekly unit			1.005 (1.0 to 1.01)	0.2
Mean ALT (n = 2070)				
Per IU/ml			1.001 (1.0 to 1.002)	0.1
PCR (n = 2251)				
Positive	69	1861	2.47 (0.9 to 6.8)	0.08
Negative	4	317	Ref	
Genotype (n = 1752)				
PCR negative	4	320	Ref	0.3
1	17	623	1.8 (0.6 to 5.3)	
2	5	114	2.1 (0.6 to 8.0)	
3	21	604	2.8 (1.0 to 8.1)	
4	2	29	4.9 (0.9 to 28.0)	
5	3	10	10.3 (2.2 to 47.0)	
Hepatitis B (n = 1691)				
Ever infected	27	587	1.2 (0.7 to 2.0)	0.6
Never infected	27	1050	Ref	
Worst Ishak fibrosis score (n = 2271)				
0	1	399	Ref	<0.001
1	3	338	3.1 (0.3 to 30)	
2	1	156	1.9 (0.1 to 31)	
3	2	136	3.9 (0.4 to 43)	
4	1	55	2.4 (0.1 to 41)	
5	8	90	17.3 (2.1 to 139)	
6	38	114	51.1 (6.9 to 377)	
No biopsy	20	909	8.1 (1.1 to 61)	
Any treatment (n = 2271)				
Yes	38	792	1.3 (0.8 to 2.1)	0.3
No	36	1405	Ref	
Treatment (n = 2271)				
Ribavirin+PEG-IFN	12	554	0.7 (0.3 to 1.3)	<0.001
IFN+ribavirin	7	126	1.7 (0.8 to 3.9)	
IFN	19	112	2.8 (1.6 to 4.9)	
None	36	1405	Ref	

2271 patients represents the whole cohort of 2285 patients minus 14 where cause of death is unascertained.

(younger) and non-drug users (older) in our cohort, such that deaths in the latter group arising from liver disease and common unrelated medical causes are predominant.

Survival in patients with chronic infection was similar to that in the small cohort of patients exposed to HCV who cleared infection spontaneously ("always PCR negative"). Of the 21 PCR-negative patients who died, the category of death was lifestyle-related in six, liver-related in four, unrelated medical in seven and unknown in four. Of the liver-related deaths, two death certificates mentioned chronic alcohol use and another patient had chronic hepatitis B. While the numbers are too small for a conclusion to be reached, these results indicate that HCV-infected patients who spontaneously clear their infection share the same lifestyle risks (including drug-related complications, suicide, murder, alcohol consumption) as those who become chronically infected. Hepatitis B infection, whether cleared infection or in a chronic carrier, had no effect on survival although there are only 65 HBV surface antigen-positive patients in this cohort. HBV co-infection has been suggested by others to worsen prognosis.²⁰

One possible source of bias in an observational study such as ours is the inclusion of patients with more severe liver disease who have HCV diagnosed because they present with liver disease-related complications, leading to an apparent increase in mortality in the short term. We have minimised this potential bias by ensuring at least 1 year of follow-up: 26 patients who died within a year of diagnosis were excluded from analysis. The average follow-up period for the cohort is over 6.7 years and exceeds 10 years for 19%. Further, the substantial proportion of non-liver-related deaths suggests this is at best only a partial explanation of the high mortality rate.

Increased age and male gender were associated with all-cause mortality and age with liver-related mortality. This is typical of nearly all survival analyses. In addition, there is considerable evidence that women, especially young women, have a good prognosis with respect to HCV infection.^{7,8} How much this is due to other factors such as low alcohol consumption, and other co-factors, is less clear. Multivariate analysis demonstrated that more severe liver damage was significantly associated with all-cause mortality and was the

Table 8 Multivariate analysis for liver mortality

	Hazard ratio (95% CI)	p Value
Gender		
Male	1.42 (0.7 to 2.6)	NS
Female	Ref	
Age		
Per year	1.042 (1.02 to 1.06)	<0.001
Mean alcohol		
Per weekly unit	1.007 (1.0 to 1.02)	0.04
Treatment		
Ribavirin+PEG-IFN	0.5 (0.2 to 1.1)	0.014
Ribavirin+IFN	1.1 (0.4 to 3.0)	
IFN	2.0 (1.0 to 4.1)	
None	Ref	
Most severe Ishak fibrosis score		
0	Ref	<0.001
1	3.6 (0.4 to 36)	
2	2.7 (0.2 to 44)	
3	5.1 (0.4 to 59)	
4	5.9 (0.3 to 105)	
5	15.7 (1.7-146)	
6	61.7 (7.8 to 490)	
No biopsy	7.1 (0.9 to 57)	

dominant predictor of liver-related mortality. This effect was seen with an Ishak fibrosis score of 4 or more. This suggests that liver biopsy findings still retain a significant role as a measure of prognosis.

The effect of treatment on survival is difficult to analyse, as there are a number of important confounders. Treatment modalities have changed over time, as have the criteria by which patients qualify for treatment. Early treatment (interferon alone) was reserved only for patients with severe liver disease who are at significantly increased risk of mortality. Thus, any potential small benefit of earlier treatments could have been cancelled out by the worse prognosis of advanced disease. Overall, however, completion of a course of therapy was clearly associated with survival from all-cause and liver-related mortality, even in those patients who subsequently relapsed virologically (table 5). This apparently surprising result may be because the ability to complete a course of therapy is a surrogate marker of a health-conscious patient who adheres to medical advice such as reducing alcohol consumption and adoption of a healthier lifestyle. The most pertinent question, however, is whether combination therapy with pegylated interferons and ribavirin prolongs survival, and the extent to which this is dependent on treatment response. This modality has only been available since 2001 and patients receiving this therapy will therefore be more likely to survive simply because they have undergone shorter periods of follow-up. In our analyses of 350 treatment-naïve patients who received combination therapy (10 deaths), there was a suggestion of benefit for both full and partial responders similar to that seen for the whole cohort. Long-term follow-up will be required to resolve this issue.

Interestingly, current alcohol consumption after diagnosis did not affect overall survival (tables 5 and 6) but unsurprisingly did predict liver mortality independently of liver biopsy findings (tables 7 and 8). We know that many of our cohort patients reduce their alcohol consumption significantly after the diagnosis of HCV infection is made,³ suggesting that alcohol reduction strategies could improve the prognosis of HCV-infected individuals. We acknowledge that accurate measurement of alcohol intake is notoriously difficult, but any misclassification bias would typically reduce the magnitude of any effect.

A number of variables significant in the univariate analyses did not emerge as independently significant after controlling for liver biopsy and treatment. Many of these factors are likely

Table 9 All-cause mortality and treatment response for patients only treated with pegylated interferon and ribavirin

	Hazard ratio (95% CI)	p Value
Gender		
Male	2.67 (0.3 to 23)	NS
Female	Ref	
Age		
Per year	1.028 (0.97 to 1.13)	NS
Response to therapy		
No response	Ref	0.04
Sustained viral response	0.10 (0.01 to 0.9)	
Relapse after initial response	0.29 (0.03 to 2.6)	

to act through liver damage and therefore become reflected in the fibrosis score.

Age at infection has been well documented to affect prognosis,^{3-5 10} but for the vast majority of HCV-infected patients this can only be estimated from knowledge of first exposure to risk. Even this estimate is not possible for a number of our cohort for whom no route of infection has been determined. Most of our cohort are likely to have been infected due to drug use in and around their twenties. With the elimination of most other routes of infection, this age group is most at risk and therefore the most important in which to describe long-term prognosis.

Knowledge of long-term disease progression and mortality rates is essential for health planning. An important incidental finding in this study is that, overall, only 23% of deaths had HCV mentioned on the death certificate, rising to just over 50% for deaths from chronic liver disease and HCC, despite the fact that the patients were enrolled in a cohort study for hepatitis C. Further, the majority of patient deaths occurred in the hospital they attended for the management of their HCV infection, and therefore the medical records (paper or electronic) should have been available to the person completing the death certificate. Thus, health planning exercises that rely on data present in death certificates will be highly inaccurate in the specific instance of HCV infection. The recent rise in liver cirrhosis deaths in the UK²¹ and elsewhere which has been attributed to alcohol may indeed include a significant proportion where HCV was an additional major, but unmentioned, factor, either on its own or as a co-factor in alcoholic liver disease.

In summary, mortality in HCV-infected patients is substantially higher than that of control populations, particularly in those younger people where the lifestyles associated with the acquisition of HCV carry increased risk. As patients age, however, there is clear evidence of excess mortality from liver-related death (fig 1) and this is likely to significantly increase as the cohort ages and liver damage progresses. Further, for the reasons discussed above, mortality rates in our cohort are likely to underestimate the actual rates in the HCV-infected population in the UK. Our results are important in planning national strategies in response to the burden of HCV infection.

Authors' affiliations

Keith R Neal, Department of Epidemiology and Public Health, University of Nottingham, Nottingham, UK

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Writing committee: Dr Keith R Neal; Ms Sheena Ramsay, Department of Epidemiology and Public Health, University of Nottingham; Dr Brian J Thomson; Professor William L Irving, Department of Microbiology and Infectious Diseases, University of Nottingham.

*The Trent Hepatitis C Study Group: Derby City Hospital: Dr A Austin, Consultant Gastroenterologist; Dr JG Freeman, Consultant Gastroenterologist; Mrs M Jackson, Hepatitis Specialist Nurse; Leicester Royal Infirmary/University of Leicester: Dr A McGregor, Consultant Histopathologist; Ms J Laurenti, Specialist Hepatitis Nurse; Professor KR Nicholson, Consultant in Infectious Diseases; Dr M Wiselka, Senior Lecturer in Infectious Diseases; Lincoln County Hospital: Dr J Harvey, Consultant Histopathologist; Dr BB Scott, Consultant Gastroenterologist; Nottingham University Hospital/University of Nottingham: Dr DA Ansell, Consultant Histopathologist; Professor RG Finch, Professor of Infectious Diseases; Ms K Jack, Specialist Hepatitis Nurse; Mrs M Holliday, Specialist Hepatitis Nurse; Professor WL Irving, Professor of Virology (Chair); Dr KR Neal, Senior Lecturer in P H Medicine & Epidemiology; Ms M Nicholls, Specialist Hepatitis Nurse; Ms S Ratib, Trent HCV Study Co-ordinator; Dr SD Ryder, Consultant Hepatologist; Dr BJ Thomson, Senior Lecturer in Infectious Diseases; Dr A Zaitoun, Consultant Histopathologist; National Blood Authority, Trent Centre: Dr DA Jones, Consultant Haematologist (Group Secretary); Royal Hallamshire Hospital, Sheffield/University of Sheffield: Dr J Bremner, Consultant Virologist, Sheffield Virology Consortium; Dr A Dube, Consultant Histopathologist; Ms J Fryer, Specialist Hepatitis Nurse; Dr D Gleeson, Consultant Gastroenterologist; Professor S Green, Consultant in Infectious Diseases; Mr G Harrison, Data Manager; Professor G Kudesia, Consultant Virologist, Sheffield Virology Consortium; Ms E McFarlane, Specialist Hepatitis Nurse; Professor MW McKendrick, Consultant in Infectious Diseases; Mr R Poll, Consultant Nurse Specialist; Mrs F Rayner, Specialist Hepatitis Nurse; Professor Sir JCE Underwood, Professor of Pathology; Dr S Whittaker, Clinical Psychologist; St James's University Hospital, Leeds: Dr C Millson, Consultant Hepatologist; Mrs S Sheridan, Specialist Hepatitis Nurse; Ms C Wigglesworth, Specialist Hepatitis Nurse; Dr J Wyatt, Consultant Histopathologist.

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