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EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Mortality in patients with chronic and cleared hepatitis C viral infection: A nationwide cohort study

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Background & Aims: It is unknown whether mortality differs between patients with chronic hepatitis C virus (HCV) replication and those who cleared the virus after infection. We examined the impact of chronic HCV replication on mortality among Danish patients testing positive for HCV antibodies.

Methods: This nationwide cohort study focused on Danish patients with at least one HCV RNA measurement available after testing positive for HCV antibodies between 1996 and 2005. To capture long-term prognosis, eligible patients needed to be alive 1 year after HCV RNA assessment. We estimated mortality rate ratios (MRRs) using Cox regression (for overall mortality) and subdistribution hazard ratios (SDHRs) for cause-specific mortality, controlling for gender, age, comorbidity, calendar period, alcohol abuse, injection drug use, and income.

Results: Of the 6292 patients under study, 63% had chronic HCV-infection and 37% had cleared the virus. Five-year survival was 86% (95% confidence interval (CI): 84–87%) in the chronic HCV group and 92% (95% CI: 91–94%) in the cleared HCV group. Chronic HCV-infection was associated with higher overall mortality (MRR: 1.55, 95% CI: 1.28–1.86) and liver-related death (SDHR: 2.42, 95% CI: 1.51–3.88). Chronic HCV-infection greatly increased the risk of death from primary liver cancer (SDHR: 16.47, 95% CI: 2.24–121.00).

Conclusions: Patients with chronic HCV-infection are at higher risk of death than patients who cleared the infection. The substantial association found between chronic HCV-infection and death from primary liver cancer supports early initiation of antiviral treatment in chronically HCV-infected patients.

Keywords: HCV; Viraemia; Mortality.

Received 15 October 2009; received in revised form 2 December 2009; accepted 3 January 2010; available online 29 March 2010

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Abbreviations: HCV, hepatitis C virus; MRR, mortality rate ratio; SDHR, subdistribution hazard ratio; CI, confidence interval; DANVIR, Danish HCV cohort; DNPR, Danish National Patient Registry; ICD, International Classification of Diseases; IDU, injection drug use; CRS, Civil Registration System; DRCD, Danish Registry of Causes of Death; RDT, registry of drug abusers undergoing treatment; IDA, Integrated Database for Labour Market Research; CCI, Charlson Comorbidity Index; MR, mortality rate; PYR, person-years of observation.

Introduction

With 170 million persons infected worldwide, hepatitis C virus (HCV) infection poses serious challenges to global health [1]. Chronic HCV replication may cause liver fibrosis, which can progress to cirrhosis, primary liver cancer and ultimately death [2]. Compared to patients with chronic HCV-infection, patients who clear the virus are at a lower risk of liver fibrosis [3] and thereby presumably at lower risk of death.

Recent studies have reported excess mortality in HCV-infected patients compared to the general population [4,5]. The clinical course of chronic HCV, however, is still debated [6]. The Trent study from the United Kingdom conducted by Neal et al. [5], which assessed predictors for death in HCV-infected patients, found that positive vs. negative HCV RNA status (i.e., viraemia vs. no viraemia) did not affect all-cause mortality. However, as the Trent cohort consisted of patients from selected referral centres, this finding might not be widely applicable [5,7]. Furthermore, the Trent study's sample size and number of events (2285 patients with 178 deaths) may have resulted in imprecise estimates of the association between HCV viraemia and mortality. Valid estimates of this association are needed to improve our understanding of chronic HCV-infection and to guide the care of HCV-infected patients after HCV RNA testing.

We therefore conducted a nationwide cohort study in Denmark to examine the association between HCV viraemia and mortality among patients testing positive for HCV antibodies.

Materials and methods

Setting

Denmark has a population of 5.4 million [8] with an estimated HCV prevalence of 0.3% [9]. Treatment of HCV-infected patients takes place in hospital departments specialised in infectious diseases, gastroenterology or hepatology [10]. Although medical care, including antiviral treatment, is provided free-of-charge to all HCV-infected residents of Denmark, only 2% of the Danish HCV-infected population has been treated with interferon [11].

Data sources

We used the unique 10-digit civil registration number assigned to all individuals in Denmark [12] to link the data sources described below.

Danish HCV cohort (DANVIR)
HCV-infected patients were identified from the DANVIR cohort, which includes all patients tested for HCV in 14 out of the 18 laboratories that perform such testing in Denmark. The cohort is estimated to include more than 90% of all Danish patients tested for HCV RNA [13]. Data collected include results and dates of HCV antibody tests (from 1991 onwards) and HCV RNA tests (from 1995 onwards). While HCV antibody tests were performed in all participating DANVIR centres, most of the HCV RNA measurements were done in one centre (Department of Clinical Biochemistry, Aalborg University Hospital), as described previously [14].

Danish National Patient Registry (DNPR)
DNPR, established in 1977, collects information on all non-psychiatric hospital admissions in Denmark. Data from outpatient and emergency department visits have been included since 1995. For each contact, DNPR records dates of admission and discharge and up to 20 discharge diagnoses, assigned by physicians and coded according to the *International Classification of Diseases*, 8th revision (ICD-8) through 1993 and the 10th version (ICD-10) from 1994 onward [15]. We extracted data from the DNPR on patients' comorbidities (including HIV coinfection), alcohol abuse, injection drug use (IDU), emergency room visits, and hospital admissions.

Civil Registration System (CRS)
CRS, established in 1968, stores information on vital status and migration for all Danish residents [12]. This data source provided information on dates of death.

Danish Registry of Causes of Death (DRCD)
DRCD contains information from all Danish death certificates issued since 1943. Computerized and validated Registry information is currently available through 2006 [16]. Whenever a Danish resident dies, the attending physician must report the cause of death; the chain of events leading to death can be described by specifying up to four diagnoses. Causes of death recorded during the study period were coded using ICD-10.

Registry of Drug Abusers Undergoing Treatment (RDT)
RDT contains information on all individuals in Denmark who received therapy for drug addiction after 1996 [17]. Treatment of drug addiction in Denmark occurs only in referral centres, which provide data to the RDT. We procured data on IDU from the RDT.

Integrated Database for Labour Market Research (IDA)
IDA, maintained by Statistics Denmark, covers Denmark's entire population [18]. Information in IDA includes (but is not restricted to) income. Data have been updated annually since 1980.

Study population

To be eligible for our study, patients in DANVIR had to meet the following criteria: (a) positive test for HCV antibodies, (b) test for HCV RNA available on or after the first positive antibody test, (c) age 20 years or older when tested for HCV RNA, (d) no HIV diagnosis before the HCV RNA test (as HIV coinfection is associated with increased mortality [13]) and (e) alive on the *index date*, defined as 1 year after the date of the HCV RNA test. The study included all DANVIR participants fulfilling these criteria from 1 January 1996 until 31 December 2005. As our main focus was long-term prognosis, we began follow up 1 year following the HCV RNA test. This delay in enrollment allowed us to avoid potential bias caused by higher rates of HCV RNA testing in patients with major morbidities who died less than 1 year following the test. We classified patients as having chronic HCV-infection (positive HCV RNA) or cleared HCV-infection (negative HCV RNA) based on their first HCV RNA test on or after the HCV diagnosis date. Patients retained their initial classification regardless of the results of further testing.

Information on study participants

Comorbidity
Comorbidity was measured using a modified Charlson Comorbidity Index (CCI) score derived from diagnoses registered in the DNPR prior to the first HCV RNA test date [19,20]. The CCI assigns a score between one and six to a range of diseases, with the sum of individual scores serving as a measure of patients' comorbidity. We defined comorbid diseases using the ICD-10 codes provided by Quan et al. [21] (matching ICD-8 codes to ICD-10 codes as closely as possible). In the present study, liver diseases were regarded as complications in the clinical pathway of HCV-infection and therefore not included in the CCI. Three comorbidity levels were defined: none (CCI score = 0), medium (CCI score = 1–2) or high (CCI score > 2).

Alcohol abuse and HIV infection
Information on alcohol abuse and HIV infection was obtained from DNPR (see Appendix 1 for details).

Injection drug use
To be characterized as having IDU a patient had to be registered in RDT and/or have a DNPR record of one or more diagnoses suggesting IDU prior to the date of HCV RNA measurement (see Appendix 1 for details).

Liver disease other than HCV
We characterised study participants by history (yes/no) of liver disease (other than HCV). We included mild and moderate to severe liver diseases in line with the CCI (see Appendix 1 for details).

Yearly income
We extracted yearly income from IDA in the calendar year preceding HCV RNA assessment, characterizing it as 0–24%, 25–49%, 50–74%, 75–99%, and 100+% of the average income in the same calendar year for all Danish citizens of the same age and gender.

Emergency room visits and hospital admissions
We characterised patients according to whether or not they had been hospitalized or visited an emergency room in the year leading up to HCV RNA measurement.

Cause of death
Based on the diagnosis listed as the primary cause of death, we categorized deaths into one of four *main* categories: liver-related deaths, non-liver-related natural deaths, unnatural deaths, or other deaths (see Appendix 2 for details).

Statistical analysis

Person-years at risk were computed from the index date until the date of death, emigration or 31 December 2006, whichever came first. Study outcomes were time to death and time to specific causes of death. The X^2 test and the Mann–Whitney *U* test were used to compare inter-group characteristics.

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All-cause mortality

We computed mortality rates (MR) with 95% confidence intervals (CI). We constructed Kaplan–Meier survival curves and used Cox regression analysis to compute mortality rate ratios (MRRs) as a measure of relative risk of death. The following covariates were included in the Cox regression models to adjust for confounding: gender, age at first HCV RNA test (20–29, 30–39, 40–49, 50–59, 60–69 or 70+ years), comorbidity (none, medium or high), year of first HCV RNA test (1996–1998, 1999–2002 or 2003–2005), alcohol abuse, IDU and income in the calendar year preceding HCV RNA assessment (0–24%, 25–49%, 50–74%, 75–99% and 100+ of average national income). Persons with missing income values were excluded from the adjusted analysis in accordance with the "complete-subject method" [22]. Schoenfeld plots confirmed that the proportional hazard assumptions were fulfilled.

To explore the generalizability of the effect of chronic HCV-infection, we repeated the analyses in subgroups defined by patients' characteristics.

Specific causes of death

We computed the cumulative incidence of specific causes of death, taking into account their status as competing risks [23]. We then used competing risks regression to obtain subdistribution hazard ratios (SDHRs) as a measure of the associations between HCV-infection and the cumulative incidence of specific causes of death [24]. We computed adjusted SDHRs for the *main* categories of causes of death (i.e., liver-related deaths, non-liver-related natural deaths, unnatural deaths or other deaths) using the same covariates as in the Cox regression (except for age, where only three categories were used (20–39, 40–69 and 70+ years)). Due to the small number of events (see Appendix 2), only unadjusted SDHRs were computed for *detailed* cause-of-death categories.

Results

Descriptive data

From the DANVIR cohort we identified 13,005 patients diagnosed with HCV, of whom 6292 met the study's inclusion criteria. Of these, 3969 patients (63%) were classified as chronically HCV-infected and 2323 (37%) as having cleared the infection. Compared to patients in the cleared group, patients with chronic HCV-infection were more likely to be male, and they also were older and had lower income, more hospitalizations, and a higher prevalence of non-HCV-related liver disease (Table 1).

Table 1. Characteristics of the 6292 HCV antibody-positive patients aged 20 years or more at the time of HCV RNA measurement, by HCV RNA status.

	HCV RNA –	HCV RNA +	*p*-Value
Patients, No. (%)	2323 (37)	3969 (63)	
Male, No. (%)	1295 (56)	2713 (68)	<0.001
Age, years, median (IQR)	38 (30–47)	40 (32–47)	<0.001
Modified Charlson Index, no. (%)			0.165
None	1933 (83)	3230 (81)	
Medium	336 (14)	628 (16)	
High	54 (2)	111 (3)	
Year of HCV RNA measurement, no. (%)			0.902
1996–1998	433 (19)	740 (19)	
1999–2002	963 (41)	1624 (41)	
2003–2005	927 (40)	1605 (40)	
Diagnosed with alcohol abuse, no. (%)	238 (10)	576 (15)	<0.001
Injection drug users, no. (%)	1043 (45)	2240 (56)	<0.001
Income (% of national average)			<0.001
0–24%	184 (8)	359 (9)	
25–49%	684 (29)	1609 (41)	
50–74%	571 (25)	1055 (27)	
75–99%	367 (16)	512 (13)	
100+%	488 (21)	374 (9)	
Missing	29 (1)	60 (2)	
Emergency room visit, no. (%)*	749 (32)	1440 (36)	0.001
Admitted to hospital, no. (%)*	613 (26)	1140 (29)	0.046
Diagnosed with liver disease (other than HCV), no. (%)†	189 (8)	444 (11%)	<0.001
Time from HCV diagnosis to first HCV RNA measurement, years, median (IQR)	0.00 (0.00–0.49)	0.10 (0.00–1.69)	<0.001

* In the year preceding the first HCV RNA measurement.
† See Appendix 1 for details.

Overall mortality

During 23,648 person-years of observation (PYR), a total of 601 patients died (MR: 25.4/1000 PYR, 95% CI: 23.5–27.5) with 448 deaths in the chronic group and 153 deaths in the cleared group. Five-year survival was 86% (95% CI: 84–87%) among patients in the chronic HCV group and 92% (95% CI: 91–94%) among those in the cleared HCV group (Fig. 1). The adjusted MRR was 1.55 (95% CI: 1.28–1.86). Chronic HCV-infection was associated with increased mortality in most subgroups, except among patients with severe comorbidity (Table 2). Restricting the cohort to patients whose positive HCV antibody test was confirmed by a 3rd generation diagnostic test prior to HCV RNA measurement ($n = 2753$) did not change the estimated association between chronic HCV-infection and mortality (data not shown).

Specific causes of death

In HCV RNA positive patients, the 8-year risks of death were: 5.5% from liver-related death, 5.5% from non-liver-related natural death, 8.8% from unnatural death, and 0.8% from other death. In HCV RNA negative patients these estimates were 2.0%, for liver-related death, 5.0% for non-liver-related natural death, 6.6% for unnatural death, and 0.2% for other death (Fig. 2). The risk of death other than liver-related death (i.e. non-liver-related death, unnatural death and other death) thereby far exceeded the risk of liver-related death for both HCV RNA positive and negative patients (15.1% vs. 5.5% and 11.8% vs. 2.0%, respectively). The corresponding causes for specific MRs are provided in Supplementary Table 1.

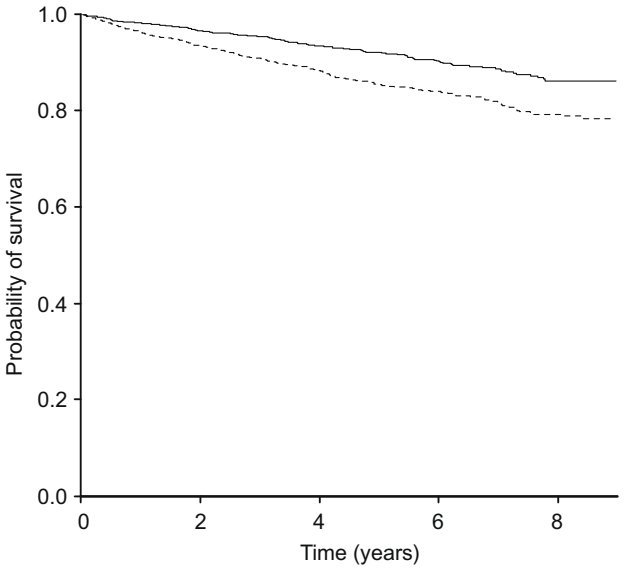

Fig. 1. Kaplan–Meier curves for HCV-infected patients. Solid line: patients with cleared HCV-infection; broken line: patients with chronic HCV-infection.

Table 2. Mortality rate ratios (MRRs) for patients with chronic HCV-infection compared to patients with cleared HCV-infection by patient subgroups. MRRs were adjusted for gender, age, comorbidity, calendar period, alcohol abuse, IDU, and income (patients with missing values for income (n = 89) were excluded from the adjusted analysis).

Patient group	n	Unadjusted MRR (95% CI)	Adjusted MRR (95% CI)
Total	6292	1.79 (1.49–2.16)	1.55 (1.28–1.86)
Sex			
Female	2284	1.80 (1.29–2.51)	1.62 (1.16–2.27)
Male	4008	1.71 (1.37–2.13)	1.50 (1.20–1.88)
Age			
20–39 years	3365	1.53 (1.16–2.02)	1.36 (1.03–1.81)
40+ years	2927	1.88 (1.47–2.40)	1.71 (1.33–2.22)
Modified CCI			
None	5163	1.89 (1.51–2.38)	1.58 (1.26–1.99)
Medium	964	1.75 (1.19–2.57)	1.80 (1.21–2.66)
High	165	0.95 (0.54–1.66)	0.94 (0.51–1.72)*
Time of first HCV RNA test			
1996–1998	1173	1.50 (1.10–2.04)	1.39 (1.02–1.91)
1999–2002	2587	1.85 (1.43–2.40)	1.55 (1.19–2.02)
2003–2005	2532	2.45 (1.49–4.05)	1.84 (1.10–3.09)
Alcohol abuse			
No	5478	1.84 (1.48–2.30)	1.65 (1.32–2.07)
Yes	814	1.38 (0.99–1.91)	1.19 (0.84–1.68)
IDU			
No	3009	2.05 (1.56–2.69)	1.61 (1.22–2.13)
Yes	3283	1.57 (1.22–2.01)	1.43 (1.11–1.84)
Liver disease			
No	5659	1.68 (1.37–2.05)	1.50 (1.23–1.85)
Yes	633	2.09 (1.32–3.33)	1.53 (0.96–2.46)
Emergency room visit			
No	4103	2.02 (1.57–2.60)	1.80 (1.40–2.33)
Yes	2189	1.49 (1.14–1.95)	1.27 (0.97–1.67)
Admitted to hospital			
No	4539	2.13 (1.65–2.76)	1.81 (1.39–2.35)
Yes	1753	1.42 (1.09–1.85)	1.25 (0.95–1.63)

* Because of few events, we used a reduced model with the following income categories: 0–49%, 50–99% and 100+% of national average.

Chronic HCV-infection was primarily associated with liver-related death (SDHR: 2.42, 95% CI: 1.51–3.88), and to some extent with non-liver-related natural causes of death (SDHR: 1.24, 95% CI: 0.91–1.71) and unnatural causes of death (SDHR: 1.28, 95% CI: 0.97–1.69). In the non-liver-related natural death category, none of the detailed causes of death were notably associated with chronic HCV-infection (Table 3). Except for primary liver cancer, there was no substantially increased risk of death due to neoplasms (SDHR: 1.28, 95% CI: 0.65–2.54).

Of the liver-related deaths, death due to alcoholic liver disease was the most frequent (2.3% vs. 1.4% after 8 years of follow-up for patients with chronic vs. cleared HCV-infection). Chronic HCV-infection was substantially associated with death from primary liver cancer (SDHR: 16.47, 95% CI: 2.24–121). However, death from primary liver cancer was rather infrequent (28 events vs. 1 event for patients with chronic vs. cleared HCV-infection, corresponding to an 8-year risk of 1.4% in patients with chronic HCV-infection and of 0.0% in patients with cleared HCV-infection) (Fig. 3). There were no deaths due to oesophageal or gastric varices.

Discussion

We observed an increased mortality among patients with chronic HCV-infection compared to patients with cleared infection, based on HCV RNA testing. This effect was observed in all patient subgroups except in those with severe comorbidity. Chronic HCV-infection was associated with liver-related mortality, and in particular death from primary liver cancer. However, the risk of deaths other than liver-related deaths by far exceeded the risk of liver-related deaths in both HCV RNA positive and HCV RNA negative patients. To our knowledge, no previous study has addressed the impact of chronic HCV replication on mortality in an equivalent nationwide setting with a long and complete follow-up and with an extensive control of confounders.

Our study has several limitations. We had access to the exact date of HCV diagnosis, but not the date of HCV-infection [6]. For a substantial proportion of study participants, HCV-infection could have preceded study inclusion by several years, since most HCV-infections occur subclinically [6]. Thus patients in the chronic group could have had more liver damage at the time of study inclusion than patients in the cleared group. We did not have access to liver biopsies or liver function tests, so we could not directly address this question. More patients in the chronic HCV group than in the cleared group were diagnosed with liver diseases other than HCV. However, we were able to demonstrate that chronic HCV-infection was associated with mortality in patients both with and without pre-existing liver diseases, which indicates that severity of liver disease did not explain our findings. Our analyses did not account for spontaneous or treatment-related viral clearance nor HCV re-infection during follow-up. Most patients are IDUs, and probably as a result, regular testing for HCV RNA subsequent to an initial diagnosis is not performed systematically in Denmark. Modelling HCV viraemia as a time-updated variable thus was not possible in this study. However, spontaneous clearance of HCV-infection subsequent to the initial acute phase of the disease occurs infrequently [25] and only a minority of Danish patients receive antiviral treatment [11]. Finally, despite the large study population and long-term follow up, our study had too small power to make statistically significant estimates for most of the detailed categories of causes of death.

Patients with chronic HCV-infection were at an increased risk of liver-related death, with the strongest association observed between chronic HCV-infection and primary liver cancer. This information is important, and suggests that clearance of the virus almost eliminates the risk of developing primary liver cancer, thus confirming the potential benefit of antiviral treatment. However, one patient in the cleared group developed primary liver cancer. This observation agrees with recent findings of cases of hepatocellular carcinoma in long-term viral suppression responders [26]. These data suggest that clearance of the virus substantially decreases but not fully eliminates the risk of primary liver cancer. Chronic HCV-infection was also associated with other liver-related causes of death (viral hepatitis, alcoholic liver disease and non-alcoholic liver disease), also emphasising the potential for antiviral treatment.

The associations between chronic HCV-infection and non-liver-related natural deaths, unnatural deaths and other deaths diminished when we adjusted for confounders. However, we cannot exclude the possibility of unmeasured or residual confounding. The fact that patients with chronic HCV-infection were at increased risk of unnatural deaths (and to some extent death due to infections) indicates certain risk-taking behaviour

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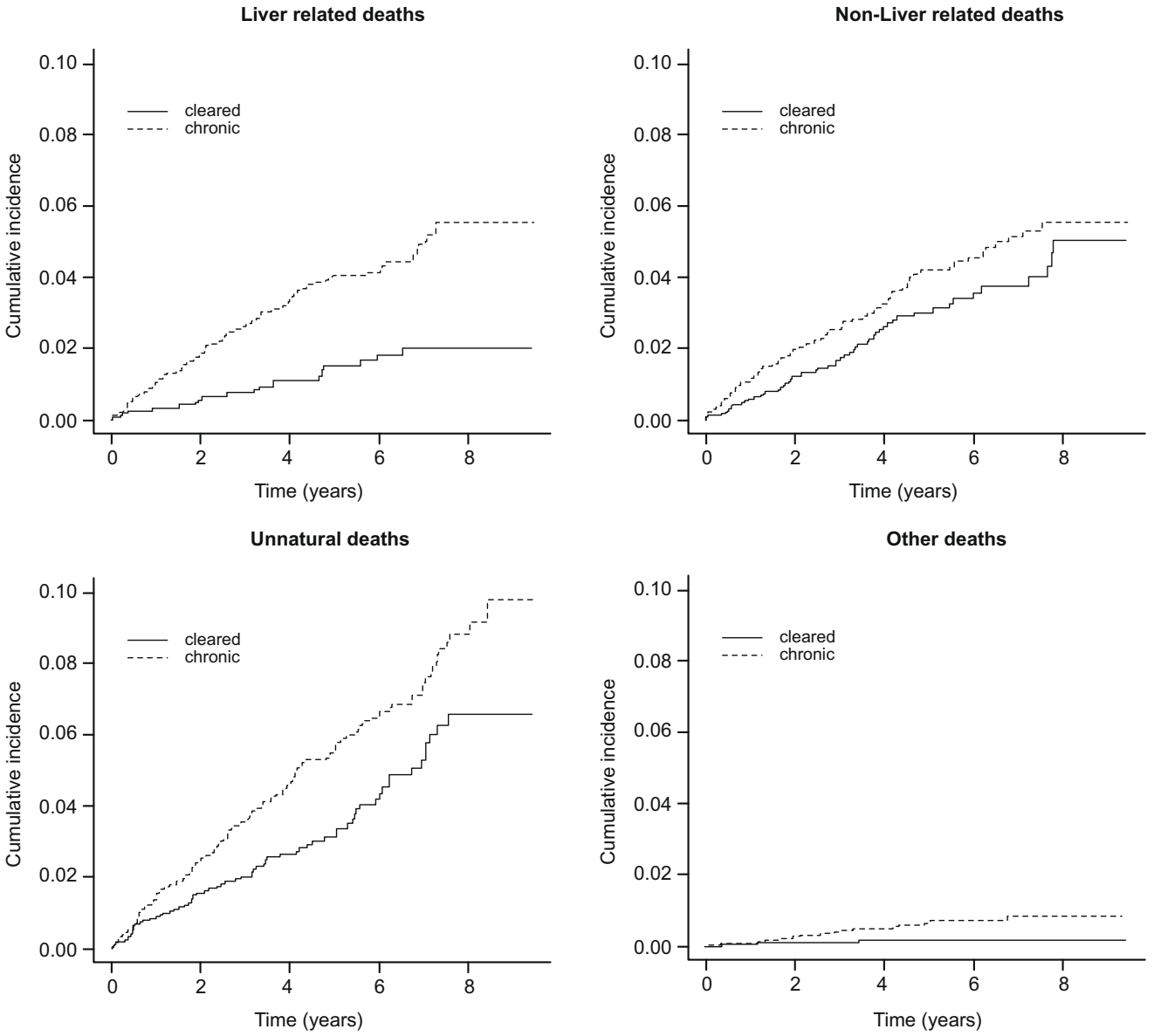

Fig. 2. Cumulative incidence of specific causes of death. Solid line: patients with cleared HCV-infection; broken line: patients with chronic HCV-infection.

in this group. As we were unable to adjust for this factor in our models, this could have resulted in unmeasured confounding. We find it likely that the associations found between chronic HCV-infection and non-liver-related natural deaths, unnatural deaths, and other deaths result from unmeasured confounding. In particular, from more injection drug use among chronically HCV-infected patients than among patients who cleared the virus.

The Trent HCV Cohort Study examined predictors of survival among HCV-infected patients treated in secondary care centres. That study, unlike ours, reported no substantial association between HCV RNA positive status (compared to HCV RNA negative status) and an increased all-cause mortality (MRR: 1.1, 95% CI 0.7–1.8) [5]. These inconsistent findings might be a result of lack of precision in the Trent study, which included only 157 deaths in the HCV RNA positive group and 21 deaths in the HCV negative group. More likely, however, these inconsistencies stem from differences in the study populations, as the Trent HCV Cohort only included patients from referral sites, while our study included nearly all patients tested for HCV RNA in Denmark. The patients in the Trent study therefore may have been at a more advanced stage of their liver disease and may have had more comorbidity. In that case, results for the Trent HCV Cohort should be compared to results for the most diseased subgroup of our study population. In fact, we did not observe a substantial impact of chronic HCV-infection among patients with a high comorbidity index, those with alcohol abuse or those who had been hospitalized recently. In a previous study from our group focusing on Danish HIV-infected IDUs with a high level of comorbidity, we also observed no association between chronic vs. cleared HCV-infection and mortality [27]. These findings suggest that chronic HCV-infection, compared to cleared HCV-infection, is associated

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Table 3. Cause-specific mortality. Due to few events, only unadjusted subdistribution hazard ratios (SDHRs) were calculated for the detailed categories of causes of death.

Main categories of death					Detailed categories of death			
Cause of death	Deaths in chronic group, n	Deaths in cleared group, n	Unadjusted SDHR (95% CI)	Adjusted SDHR (95% CI)	Cause of death	Deaths in chronic group, n	Deaths in cleared group, n	Unadjusted SDHR (95% CI)
Liver-related deaths	122	25	2.91 (1.89–4.48)	2.42 (1.51–3.88)	Viral hepatitis	35	2	10.35 (2.49–43.06)
					Primary liver cancer	28	1	16.47 (2.24–121.00)
					Alcoholic liver disease	53	20	1.57 (0.94–2.62)
					Non-alcoholic liver disease	6	2	1.79 (0.36–8.82)
Non-liver-related natural deaths	125	55	1.35 (0.98–1.85)	1.24 (0.91–1.71)	Neoplasms (excl. primary liver cancer)	26	12	1.28 (0.64–2.54)
					Miscellaneous causes of death	18	11	0.96 (0.45–2.04)
					Endocrine, nutritional, and metabolic diseases	7	7	0.59 (0.21–1.68)
					Diseases of the nervous system	10	2	2.96 (0.65–13.48)
					Diseases of the circulatory system (excl. oesophageal and gastric varices)	40	14	1.69 (0.92–3.10)
					Diseases of the respiratory system	15	4	2.21 (0.74–6.61)
					Diseases of the digestive system (excl. liver diseases)	9	5	1.06 (0.36–3.19)
Unnatural deaths	182	70	1.55 (1.18–2.04)	1.28 (0.97–1.69)	Mental and behavioural disorders due to psychoactive substance use	36	14	1.52 (0.82–2.82)
					External causes	146	56	1.55 (1.14–2.11)
Other deaths	19	3	3.75 (1.11–12.66)	2.92 (0.83–10.29)	Certain infectious and parasitic diseases (excl. viral hepatitis)	11	1	6.48 (0.84–50.11)
					Missing causes of death	8	2	2.37 (0.50–11.20)

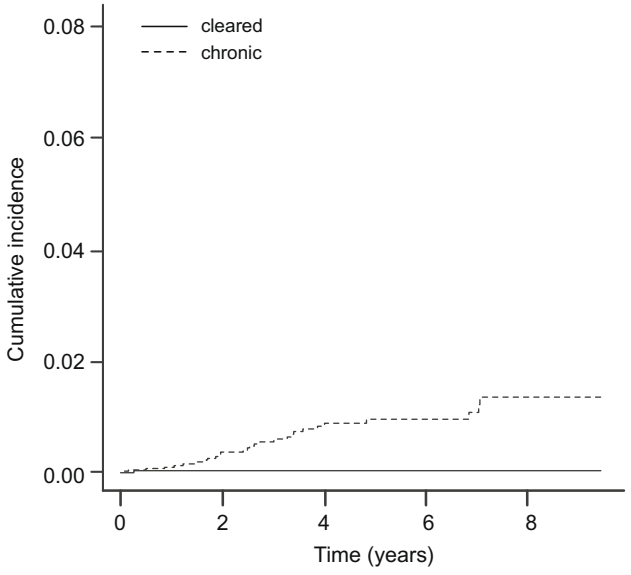

Fig. 3. Cumulative incidence of death from primary liver cancer. Solid line: patients with cleared HCV-infection; broken line: patients with chronic HCV-infection.

with increased mortality in most patient groups. However, in high-risk study populations characterised by substantial mortality, the relative impact of chronic HCV-infection is limited.

We conclude that based on HCV RNA assessment, patients with chronic HCV-infection have higher mortality and, in particular, a higher risk of liver-related death than patients who cleared the virus. The pronounced association between chronic HCV-infection and death from primary liver cancer provides a rationale for antiviral treatment in chronically HCV-infected patients. However, our data also underline the importance of a balanced decision, as subgroups characterised by substantial mortality probably have less potential for a treatment benefit.

Potential financial conflicts of interest

N. Obel has received grants from Roche, Bristol-Meyers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Abbott, Boehringer Ingelheim, Janssen-Cilag, and Swedish-Orphan Drugs.

P.B. Christensen has received grants from Roche and Scheering-Plough.

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Funding

Lars H Omland received funding for this research through a PhD scholarship from Rigshospitalets Research Council.

Acknowledgements

Centres and members of the DANVIR Cohort Study.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jhep.2010.01.033.

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