

ORIGINAL ARTICLE

Long-term follow-up among Danish transfusion recipients identified in the national hepatitis C lookback

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BACKGROUND: In 1996, a national lookback study was performed in Denmark identifying 1018 patients exposed to hepatitis C virus (HCV) by transfusion before 1991. The objective of this study was to describe morbidity and mortality during extended follow-up among patients in the Danish HCV lookback cohort alive in 1996.

STUDY DESIGN AND METHODS: In a retrospective cohort study of 230 patients exposed to HCV by blood transfusion and alive in 1996 we extracted data from national registers and compared these with a matched group of unexposed transfusion recipients.

RESULTS: Among 230 HCV-exposed recipients alive in 1996, 124 (53.9%) had chronic hepatitis C, 43 (18.7%) were not infected, and 63 (27.4%) had incomplete HCV data. In 2009, 121 (52.6%) were still alive a median of 21.8 years after transfusion. The mortality rate among the HCV-exposed recipients followed from 1996 was 4.9 per 100 person-years (PY). The incidence of liver cirrhosis and decompensated cirrhosis was 1.0 per 100 PY and 0.4 per 100 PY, respectively; 16.5% had cirrhosis at death. Among HCV-exposed recipients, no difference in all-cause or liver-related mortality was observed between HCV-infected and HCV-uninfected recipients. Further, there was no difference in mortality between HCV-exposed and -unexposed transfusion recipients (mortality rate ratio [MRR], 1.06; 95% confidence interval [CI], 0.96-1.17; $p = 0.47$), but liver-related mortality was significantly higher among HCV-exposed patients (MRR, 10.0; 95% CI, 7.20-17.7; $p < 0.001$).

CONCLUSION: Two decades after exposure to blood products from HCV-infected donors, only 121 (11.8%) of 1018 recipients remained alive. For HCV-exposed recipients no excess all-cause mortality was observed, but liver-related mortality was significantly increased.

After the introduction of hepatitis C virus antibody (anti-HCV) screening of Danish blood donors in 1991, 150 HCV-positive donors were identified, and in 1996, a national targeted hepatitis C lookback study was performed among 1018 recipients of blood from these donors, as previously reported.¹

The natural history of hepatitis C infection is still debated and complications may develop decades after infection.^{2,3} In most cohorts of patients with chronic HCV infection, the exact time of infection is not known, and many infected patients are drug users whose long-term mortality may be confounded by other causes of death including drug overdose.⁴ Thus, the study of patients

ABBREVIATIONS: HR = hazard ratio; MMR = mortality rate ratio; MR = mortality rate; PIN = personal identification number; PY = person-years.

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exposed to HCV through transfusion provided a unique possibility to describe the natural history of transfusion-transmitted chronic HCV infection.

The primary aim of this study was to determine liver-related morbidity and mortality during long-term follow-up among patients identified in the Danish HCV lookback cohort and alive in 1996. A secondary aim was to estimate how accurately this group of patients was recorded in Danish public health registers of chronic hepatitis C.

MATERIALS AND METHODS

Patient population

The study was register-based without any direct patient contact. Linkage of recipients to registers in this study was done by their personal identification number (PIN), which is a unique 10-digit code assigned to all permanent residents of Denmark.⁵

A total of 1018 HCV-exposed transfusion recipients were identified in the lookback investigation in 1996.¹ They were identified in local transfusion registers back to 1985 and for some blood banks back to 1975. Among these, 730 were dead and 288 were alive in 1996 (Fig. 1).

In the 1996 lookback cohort, PIN was only recorded for recipients alive and where the hospital responsible for transfusion supplied the PIN to the lookback group. A total of 121 of the 288 recipients alive in 1996 were not referred for hepatitis C infection evaluation by the hospital responsible for transfusion. Reasons for this were advanced age or severe comorbidity or they did not respond to the invitation for lookback evaluation. In 58 of the 121 recipients not referred to hepatitis C evaluation, the PIN was not supplied by the evaluating hospital and they could not be included in this follow-up study.

Among the 230 recipients with valid PIN included in the follow-up study, 167 were evaluated in 1996 and the remaining 63 recipients were not for the reasons mentioned above. The following information was extracted in January 2009 from national population and health registers.

Registers

The Danish Civil Registration System provided information on vital and emigration status.⁵ The Hospital Discharge Diagnose Register includes all diagnosed inpatients from 1977 and outpatients from 1995.⁶ Until 1993, diagnoses were coded according to the International Classification of Diseases, 8th revision (ICD-8), and from 1994 according to the 10th revision (ICD-10). For all recipients the register provided diagnosis codes and dates for all hospital contacts. This information was used to calculate the Charlson comorbidity index, which predicts the 1-year mortality based on patients' comorbid conditions (a total

1996 Lookback:

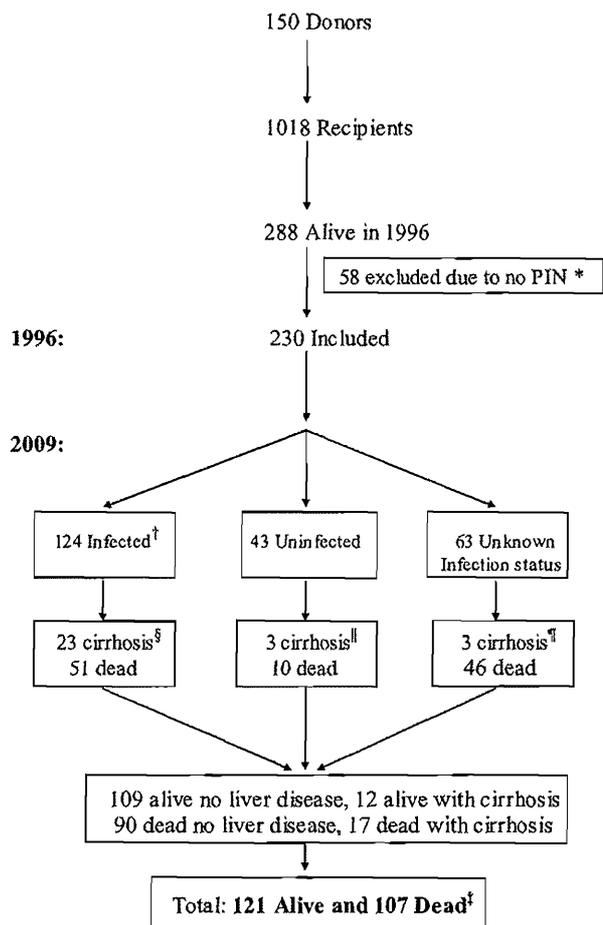


Fig. 1. Flow chart of recipients identified in the 1996 lookback study. †For definitions of infected, uninfected, and unknown infection status see Materials and Methods. ‡Excluding two that left the country during follow-up. §Excluding two cases of cirrhosis, due to cirrhosis before transfusion. ||Excluding one case of cirrhosis, due to cirrhosis before transfusion. ¶Excluding three cases of cirrhosis, one due to missing transfusion date and two due to cirrhosis before transfusion.

of 22 conditions).⁷ The Charlson comorbidity index was calculated at time of transfusion, at time of lookback investigation in 1996 and at end of follow-up (at time of death or January 1, 2009, whichever came first).

The Cause of Death Register provided causes of death as recorded on death certificates.⁸ For exposed recipients, results of HCV RNA and anti-HCV tests were extracted from DANVIR.⁹ This national research database contains information on all patients tested for hepatitis C in 14 of the 18 Danish laboratories performing HCV testing and is estimated to cover 85% of the Danish population tested for anti-HCV (P.B. Christensen, personal communication, 2010).

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The Danish Database for Hepatitis B and C (DANHEP) is a nationwide database, which includes data on all patients older than 16 years of age who have received clinical care for chronic viral hepatitis B and C since 2002.¹⁰ The database provided detailed information on demographics, morbidity, treatment history, and mortality.¹¹

The PATOBANK register provided results of all pathology examinations from Danish hospitals since 1997.¹² The National Register of Notifiable Diseases provided the mandatory report forms from the diagnosing physician of acute viral hepatitis (from 1980) and chronic viral hepatitis B and C (from May 2000).¹³ The register has been estimated to cover 35% to 40% of clinical cases.^{14,15} Information extracted from the registers was combined with information collected during the lookback study. ICD-8 and ICD-10 codes, used to search the data from the Hospital Discharge Diagnose Register and the Cause of Death Register, are provided in the supplementary material (Appendices Table S2, available as supporting information in the online version of this paper).

From the Danish part of Scandinavian donation and transfusion (SCANDAT) database,¹⁶ which contains data from transfusion registers in Sweden and Denmark, unexposed transfusion recipients who were alive in January 1996 were matched (4:1) to the HCV-exposed recipients on sex, age (mean absolute difference, 175 days; standard deviation [SD], 191 days) and transfusion date (mean, 15.5 days; SD, 19.7 days). Information on transfusion date was missing for one HCV-exposed recipient; 916 unexposed transfusion recipients were matched to the remaining 229 HCV-exposed recipients.

Exposure and outcome classification

Among HCV-exposed recipients chronic hepatitis C was defined by one or more of the following criteria: positive for HCV RNA, more than 6 months after suspected exposure; hospitalized for chronic hepatitis C according to the Hospital Discharge Diagnose Register and/or registered with chronic hepatitis C in The National Register of Notifiable Diseases, The Danish Database for Hepatitis B and C, or PATOBANK. Exposed recipients with negative HCV RNA test irrespective of result of anti-HCV test or with unknown HCV RNA and negative anti-HCV test were considered HCV uninfected. HCV-exposed recipients not fulfilling the criteria for neither infected nor uninfected recipients were classified as having unknown HCV status. Deaths were classified as liver related when the death certificate stated cirrhosis, decompensated cirrhosis, varices, ascites, or hepatocellular carcinoma as primary cause of death.

Statistical analysis

The start of observation for all statistical analyses was January 1, 1996, and the end of follow-up was time of

death or January 1, 2009, whichever came first. Age in the statistical analysis is defined as age at the time of lookback investigation, January 1, 1996. The Charlson comorbidity index value used in the statistical analysis was also calculated based on data from January 1, 1996.

The Mann-Whitney test was used to compare quantitative variables. Cox regression analysis was used to assess the effect of hepatitis C infection and treatment among the HCV-exposed recipients on all-cause mortality, liver-related disease, and liver-related mortality controlling for Charlson comorbidity index and age. Tests based on Schoenfeld residuals showed that the proportional hazard assumption was satisfied by the variables used in the Cox regression model.

Survival of HCV-exposed transfusion recipients (regardless of HCV status, $n = 229$) and matched unexposed transfusion recipients ($n = 916$) were illustrated by Kaplan-Meier curves and compared using log-rank test. HCV-exposed recipients with documented HCV infection ($n = 124$) were compared with matched unexposed transfusion recipients ($n = 496$), using the same methods.

Data were analyzed using computer software (Stata, Version 11.0, StataCorp, College Station, TX; and SAS, Version 9.1, SAS Institute, Cary, NC). p -values of less than 0.05 were considered significant. This study and the SCANDAT register were approved by the Danish Data Protection Agency with, respectively, Journal 2008-41-2355 and Journal 2001-41-1403.

RESULTS

Of the 230 HCV-exposed transfusion recipients alive in 1996, 121 (53%) were alive in 2009, corresponding to 11.8% of the 1018 exposed recipients originally identified in the Danish HCV lookback (Table 1).¹ The median age of the survivors was 58 years at end of follow-up (range, 21-92 years) with a median of 21.8 years since transfusion and 49.6% were male.

Among the 230 recipients alive in 1996, chronic HCV infection was documented in 124 recipients, 43 recipients were uninfected, and 63 recipients had unknown infection status according to our definitions (Fig. 1). Of 153 exposed recipients who were tested, 127 (83%) were anti-HCV positive, indicating that transmission had taken place (Table 1).

The 63 recipients with unknown infection status had not been referred to hepatitis C evaluation in the 1996 lookback. They were on average 20 years older than referred patients ($p < 0.001$), but did not differ in Charlson comorbidity index (data not shown). All 230 HCV-exposed recipients alive in 1996 were admitted to a hospital or an outpatient clinic during follow-up.

Among the 124 patients with documented HCV infection who were alive in 1996, 92 (74%) had a diagnosis

TABLE 1. Characteristics of the 230 HCV-exposed recipients alive in 1996 at time of follow-up

Characteristics	Recipients (n = 230)
Male gender	121 (53%)
Alive January 2009	121 (53%)
Mean age at transfusion (years)*	48 (0-89)
Mean years since transfusion*†	18 (4-34)
Anti-HCV positive n/total tested (%)	127/153 (83%)
HCV RNA positive n/total tested (%)‡	99/144 (69%)
HCV genotype 1/2/3/4 n (%) (total tested)	38 (59%)/12 (19%)/14 (22%)/0 (0%) (64)
Charlson comorbidity index in 1996 (SD)	1.1 (0.9)
Charlson comorbidity index in 2009 (SD)	1.5 (0.8)
Registered in	
Hospital Discharge Diagnose Register	230 (74%)§
National Register of Notifiable Diseases	20 (16%)§
Laboratory register (DANVIR)	87 (56%)¶
Clinical register (DANHEP)	43 (35%)¶

* One recipient had no date of transfusion reported.

† For recipients alive at follow up mean duration since transfusion was 21.8 years (range: 16-34).

‡ At least one positive HCV RNA measurement.

§ Percent registered with the HCV diagnosis of the 124 recipients with documented chronic hepatitis C.

¶ Percent registered of the 124 recipients with documented chronic hepatitis C.

of chronic hepatitis C (Table 1) and five (4%) had other liver-related disease (data not shown) in the hospital discharge diagnose register. In comparison, 56% of the infected recipients were identified in the laboratory database (DANVIR), 35% were registered in the clinical register (DANHEP), and 16% were reported to the National Register of Notifiable Diseases (Table 1). Only 15 (12%) of the 124 were registered with chronic hepatitis C in the hospital discharge diagnose register and identified in the other three registries.

The all-cause mortality rate (MR) of the 230 HCV-exposed recipients alive in 1996 was 4.91 per 100 person-years of observation (PY) and nearly identical to that of matched unexposed transfusion recipients (MR, 4.62/100 PY; mortality rate ratio [MRR], 1.06; 95% CI, 0.96-1.17; $p = 0.47$; Fig. 2). Neither did we find any significant difference in all-cause mortality when comparing the 124 HCV-infected recipients with their matched unexposed transfusion recipients (Fig. 3) or with the 43 uninfected HCV-exposed recipients, adjusted for age and Charlson comorbidity index (Table 2). Infected and uninfected recipients did not have significantly higher mortality than recipients with unknown HCV status, adjusted for age and Charlson comorbidity index ($p = 0.6$ and $p = 0.7$; data not shown).

Rates of liver-related disease and liver-related death were not significantly different between the infected and uninfected recipients, when adjusting for age and Charlson comorbidity index (hazard ratio [HR], 6.2 [0.8-47]; and HR, 1.1 [0.1-10]; Table 2). Among 107 deaths observed between 1996 and 2009 in the 230 HCV-exposed recipients 17 (16.5%) of 103 had liver disease at death (Fig. 1; excluding four deaths who had cirrhosis at the time of

transfusion) and the primary cause of death was liver related in nine recipients (8.7%; MR, 0.46/100 PY; excluding one recipient with cirrhosis before transfusion; supplementary material, Tables S3 and S4, available as supporting information in the online version of this paper). Malignancy accounted for 21% of all deaths, of whom four (4%) of 107 died of hepatocellular carcinoma and 50% died from cardiovascular disease. For HCV-exposed recipients, HCV infection was recorded but not considered a contributing cause of death in seven (6.5%) of all 107 death certificates.

Among the 916 unexposed recipients extracted from the SCANDAT register only four liver-related deaths were observed, resulting in a liver-specific MR of 0.046 per 100 PY. Thus, the liver-related MRR for HCV-exposed recipients

was 10.0 (95% CI, 7.20-17.7; $p < 0.0001$), compared with unexposed transfusion recipients matched by age, sex, and transfusion date.

Cirrhosis was found in 20 (26%) of the 79 exposed recipients who underwent histologic examination after the 1996 lookback. This included 15 (21%) of the 73 who underwent liver biopsy, four recipients with a clinical diagnosis of decompensated cirrhosis, and one recipient who had decompensated cirrhosis with ascites diagnosed at routine postmortem autopsy. Thus the observed incidence of cirrhosis among recipients between 1996 and 2009 was 1.0 per 100 PY (supplementary material, Table S1, available as supporting information in the online version of this paper).

However, autopsy was performed in only six (6%) of the 107 deceased HCV-exposed recipients. Here two recipients had decompensated cirrhosis with ascites, one not previously registered with cirrhosis or HCV infection, and one with known HCV.

Only 35 (28%) of the 124 HCV-infected recipients received treatment for hepatitis C, of whom 46% were cured (achieved sustained virologic response). Treated recipients had a significantly lower mortality than untreated ($p = 0.03$; HR, 0.3 [0.1-0.9]), but mortality was not lower among those who were cured, compared with those who were treated but not cured (HR, 0.5 [0.04-6.4]; $p = 0.57$), when adjusted for age and Charlson comorbidity index.

DISCUSSION

Thirteen years after the initial HCV lookback the vast majority of recipients have died. No increase in

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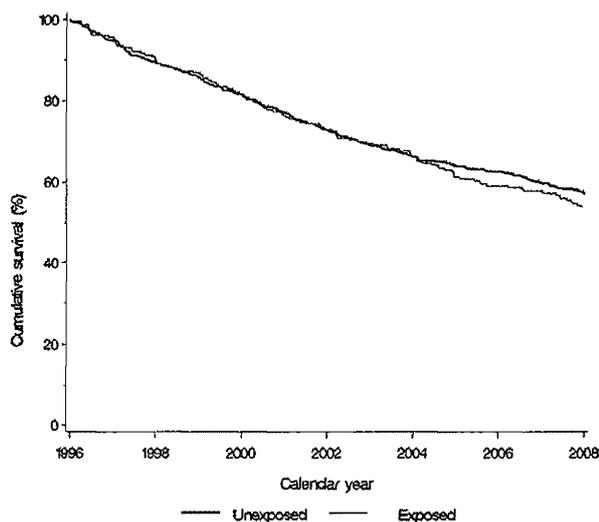


Fig. 2. Survival of HCV-exposed recipients alive in 1996 ($n = 229$) compared with non-HCV-exposed blood transfusion recipients alive in 1996 ($n = 916$) matched 4:1 by age, sex, and transfusion date. Note: Log rank test for difference $p = 0.47$.

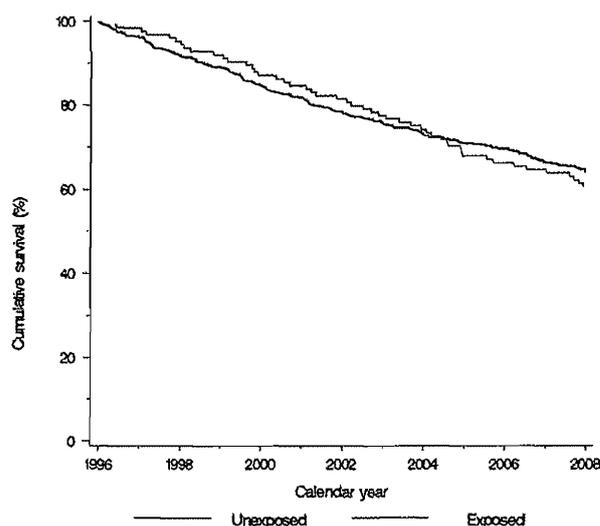


Fig. 3. Survival of recipients alive in 1996 with documented chronic HCV after transfusion ($n = 124$) compared with non-HCV-exposed blood transfusion recipients alive in 1996 ($n = 496$) matched 4:1 by age, sex, and transfusion date. Note: Log rank test for difference $p = 0.67$.

TABLE 2. Morbidity and mortality outcomes of HCV-exposed recipients with known infection status

Characteristics	Uninfected	Infected	HR (95% CI)
Total in group*	43	124	
Morbidity from 1996 lookback to 2009			
Cirrhosis	1	17	6.2 (0.8-47)†
Esophageal varices	0	2	
Ascites	2	8	0.9 (0.2-4.4)†
Hepatocellular carcinoma	0	4	
Any liver-related disease‡	1	17	6.2 (0.8-47)†
Mortality, cause of death as recorded on death certificate			
Dead in 2009	10	51	1.2 (0.6-2.4)†
Liver-related death‡	1	7	1.1 (0.1-10)†
Cardiovascular disease	6	22	0.7 (0.3-1.8)†
Cancer	2	8	1.2 (0.2-5.7)†
Narcotic abuse	1	1	0.2 (0.1-3.3)†

* Sixty-three with unknown infection status not included.

† Cox regression analysis controlling for Charlson comorbidity index in 1996 and age at time of lookback in 1996.

‡ Liver-related disease defined as cirrhosis, ascites, esophageal varices, or hepatocellular carcinoma.

all-cause mortality was observed among the HCV-exposed recipients who were still alive in 1996, but liver-related death was significantly increased. Few recipients were treated for hepatitis C and we could not demonstrate a higher survival among the cured.

There are several limitations to our study. Due to the design of the national lookback we could not identify recipients who died before 1996. Therefore, it was not possible to determine whether HCV infection affected recipient survival in the first years after transfusion. Most recipients were infected less than 10 years before the lookback in 1996 and previous follow-up studies did not find

an increased mortality in the first years of observation.^{17,18} Therefore, we believe that this was not a significant bias in our study.

The hepatitis C status of 63 (27%) exposed recipients was unknown as they were not tested for hepatitis C in the primary lookback. Their responsible physician in 1996 decided that they would not benefit from testing or the recipient did not want to participate. The members of this group were significantly older than other recipients, but when analysis was adjusted for age and Charlson index, their mortality was not significantly higher than the group with known infection.

In the original lookback HCV RNA testing was not used universally. Therefore, recipients who were anti-HCV negative and/or had normal alanine aminotransferase were less likely to be referred for follow-up during the lookback. By excluding this group of presumably more healthy patients we could potentially have overestimated the morbidity and mortality from hepatitis C. However, only 37% of identified individuals had undergone histologic evaluation and it is noteworthy that one of six deceased recipients who underwent routine autopsy had decompensated cirrhosis that was not diagnosed while the patient was alive. Thus, the true prevalence of cirrhosis could also be higher than our estimate.

The finding that recipients treated for hepatitis C had better survival than nontreated recipients was surprising because we found no increase in mortality among the hepatitis C infected. However, the number of treated patients was small and we believe that the difference observed reflects a bias in patient selection: for example, older and more vulnerable patients were less likely to receive treatment for hepatitis C during the lookback.

We found a low coverage of the hepatitis C-infected recipients in the public registers of Denmark, in agreement with previous estimates.^{9,11} This may reflect the fact that some of the registers were established several years after the HCV lookback took place, but it is nevertheless an important observation for future register-based research in hepatitis C.

The all-cause mortality in both HCV-exposed and -unexposed transfusion recipients was high, reflecting that transfusion by itself was associated with high mortality. Recently, a large Scandinavian follow-up study found a 65% 10-year MR and a 77% 20-year MR among transfusion recipients.¹⁹ Corresponding figures for the Danish HCV lookback cohort were 70 and 85%, but when comparing HCV-exposed recipients to matched unexposed transfusion recipients there was no difference in all-cause mortality. This is in agreement with previous follow-up studies of transfusion-related hepatitis C infection.^{17,20}

In contrast, a recent large Danish population-based HCV mortality study found a small (but significant) increase in mortality (relative risk, 1.5 comparing mortality among patients with chronic hepatitis C infection vs. patients with past infection).⁹ Also the large study of HCV mortality in blood donors by Guiltinan and colleagues²¹ showed only a moderate increase in overall mortality, but a similar high association with liver disease deaths.

The studies that found an increased all-cause mortality among HCV infected include only a small fraction of transfusion recipients as 85% of all hepatitis C infection in Scandinavia is associated with drug abuse.^{22,23} It may be that the observed higher all-cause mortality in the HCV-infected population could be associated to drug use and that HCV infection was a surrogate marker for this.⁴ In

contrast we found a high liver-related morbidity and MR for hepatitis C-exposed recipients, confirming our first report and in agreement with published studies.^{1,3,20,21}

It is a paradox that the HCV-related liver disease does not translate into an increased all-cause mortality. During the first decades of HCV research, this was explained by too short follow-up time in the cohorts, acknowledging that end-stage liver disease may take 20 to 30 years to develop. However, follow-up time has now prolonged into the third decade in our and other hepatitis C cohorts and the paradox remains. It may be that although the HCV-related liver disease progresses, this is over time outweighed by the competing risk of death from common diseases such as cancer and cardiac diseases—which was also the primary causes of death in our cohort.¹⁸

Two decades after exposure to a hepatitis C-positive transfusion only a small fraction of recipients were still alive. A 10-fold increase in liver-related mortality was found, but this did not result in an increase in overall mortality. Hepatitis C-positive recipients were most likely to die with, but not from, their HCV infection.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to **TRANSFUSION**.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

TABLE S1. Liver related morbidity and mortality among 230 HCV exposed recipients alive in 1996.

TABLE S2. ICD 8 and ICD 10 Codes extracted from the hospital discharge diagnose register.

TABLE S3. Registrations on death certificates according to infection status in 2009 among HCV-exposed recipients alive in 1996.

TABLE S4. Registrations in the Hospital Discharge Diagnose Register among the living in 2009, according to infection status.

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