Long term mortality outcomes in HCV-infected blood recipients: UKHSA report 2022

Introduction

Before the implementation of blood donor screening, a number of blood recipients were infected with hepatitis C virus (HCV), which slowly causes progressive liver disease (LD), and can ultimately result in death. Long term outcomes for this cohort are of interest in determining the public health impact of the infected blood incident, and outcomes in general for those infected with HCV.

Individuals known to have received HCV-infected blood were traced, and have been followed up for the past 30-40 years, with intermittent questionnaires and continuous follow up for mortality via linkage to ONS deaths. Previous analyses have found no difference in overall mortality for cases compared to uninfected controls, but have not been updated for some time.

We examined long-term outcomes in this cohort, considering overall mortality in cases vs. uninfected controls. Previous analyses are extended to consider time at risk from the date of transfusion, and examining liver disease-specific mortality compared to other causes. We also consider how additional covariates affect the outcome, which was hampered previously by potentially consequential amounts of missing data.

Methods

National Register dataset

Text below from Harris et al, BMJ 2002

At the end of 1999, 996 transfusion recipients infected with HCV had been traced during the lookback. For most patients, transfusion was the only probable route of infection, but 18 were excluded because exposure to other possible causes meant that the date they acquired the virus was uncertain (nine had injected drugs and nine had been exposed to blood products). Seventeen recipients were excluded either because they could not be flagged within the NHS central registers (11 patients), because the recipients were transfused after the testing of the blood supply for antibodies to HCV was introduced (three patients), or because their dates of counselling were not clear (three patients). A further 37 recipients were excluded because full confirmatory testing revealed that they were not infected with the virus or because initial reactivity to antibodies to HCV was not confirmed. Of the remaining 924 eligible patients, 608 (65.8%) were known to be positive for HCV ribonucleic acid and 189 (20.5%) negative for ribonucleic acid at baseline (time of first diagnostic test following transfusion). For 127 (13.7%) the status was unknown.

To provide a source of data on transfusion recipients who were HCV negative, all 536 recipients from the HCV lookback exercise in England who were traced and counselled and who tested negative for anti-HCV were identified. Four of the recipients were excluded because their records could not be flagged within the NHS central registers, and 57 because their dates of transfusion were unclear or because their transfusion took place after the introduction of anti-HCV testing of donated blood. Of the 475 controls, 443 (93%) were confirmed to be HCV ribonucleic acid negative; the ribonucleic acid status of 32 (7%) was not known.

Data were collected from patients and controls at the time of initial counselling during the HCV lookback and from death registration forms. Additional data on patients was obtained at entry into the HCV national register. To compare all-cause mortality and liver related mortality in patients and controls, we reviewed the text of the death certificates; deaths in which HCV related liver disease

was likely to have been a direct cause of death were also identified. For this we included certificates that mentioned hepatocellular carcinoma or end stage liver disease (varices, ascites, or hepatic encephalopathy) or where liver disease was coded as the underlying and only cause of death. Death certificates for which liver disease or hepatitis C were given as contributory factors were included as a separate category; decisions regarding cause of death may have been influenced by knowledge of the patient's HCV status.

Statistical analysis

All-cause mortality in cases vs. controls was considered within a survival analysis framework. Covariates included age at transfusion (<20, 10-year, and ≥80 year bands), sex, alcohol use at baseline (none, <=20 units per week, >20 units per week, unknown), ethnicity (white/non-white), country of birth (UK/non-UK) and HBV status at baseline. Baseline PCR status, ever-treatment for HCV and patient recorded as having cleared the virus were also considered, using data from the follow-up questionnaires.

All variables except age, sex and case/control status had substantial numbers of missing observations. The impact of missing data was considered via multiple imputation, using a chained equations approach, with categorical variables predicted using logit or multinomial models as appropriate. All variables were included in the prediction equations, including the cause-specific mortality variable, and 10 imputed datasets were produced.

Cox models were fitted to the data on age and other covariates. Survival time was taken from the time of transfusion, while accounting for left-truncation: individuals were only observed from the date of HCV diagnosis. Where imputed datasets were used, estimates from the multiple datasets were combined using Rubin's rules. Covariate models using the imputed dataset did not include time-varying covariates.

The competing risks model of Fine and Gray was applied to estimate hazards of liver-related mortality (direct cause, and mentioned on death certificate) while accounting for death from other causes as a competing risk.

Discrete time categorical model

The relationship between age, time at risk and cause-specific outcomes were further explored via a discrete-time multinomial model. Data were split into yearly intervals; within each interval the following multinomial outcome could occur: 1) alive, 2) died directly from liver disease, 3) died with liver disease on the death certificate, or 4) died from other causes.

Current age was included as a time-varying covariate, categorised into <20, 10-year, and ≥80 year bands. Time since transfusion was also included as a time-varying covariate, and categorised as <10, 10-20, 20-30 and 30+ years. The probability of each outcome was assumed to be constant within each time at risk/age band. Pairwise interactions between age, time at risk and case status were considered, with models compared via the AIC score. Other covariates were not included. Predicted probabilities of death from each outcome were generated from the model for cases and controls, by age and sex.

Results

Table 1 shows characteristics of the infected cohort and uninfected controls. The median age of cases was slightly older, but there was no significant difference, nor by sex. The year of transfusion

was slightly earlier for controls, although the difference in means was less than 1 year. There were differences in country of birth, ethnicity, HBV status and alcohol consumption, but largely in the amount of missing data, with more missing ethnicity and country of birth in controls than cases, but more missing HBV status and alcohol consumption in cases. 77% of cases were confirmed as PCR positive at baseline, and 30% were reported as having been treated. Of those who were treated, just over half reported achieving sustained viral response (SVR).

Table 1. Characteristics of cases and controls, age and year show median and inter-quartile range, and T-test p-value for difference in mean. Categorical variables show numbers and percentage in each category, and chi-squared p-value.

Variable	Case	Controls	p-value
N	922	475	
Age	45 (25, 61)	42 (25, 61)	0.103
Female	477 (51.7%)	249 (52.4%)	0.808
Year of transfusion	1989 (1987, 1990)	1989 (1986, 1990)	<0.001
Country of birth			
UK	742 (80.5%)	333 (70.1%)	
Other	57 (6.2%)	35 (7.4%)	
Unknown	123 (13.3%)	107 (22.5%)	<0.001
Ethnicity			
White	781 (84.7%)	325 (68.4%)	
Other	49 (5.3%)	37 (7.8%)	
Unknown	92 (10.0%)	113 (23.8%)	<0.001
Baseline PCR status			
Negative	183 (19.8%)	N/A	
Positive	709 (76.9%)		
Unknown	30 (3.3%)		.
HBV status			
Negative	626 (67.9%)	390 (82.1%)	
Positive	23 (2.5%)	8 (1.7%)	
Unknown	273 (29.6%)	77 (16.2%)	<0.001
Alcohol use at baseline (units per week)			
0	264 (28.6%)	249 (52.4%)	
<20	346 (37.5%)	181 (38.1%)	
20+	88 (9.5%)	29 (6.1%)	
Unknown	224 (24.3%)	16 (3.4%)	<0.001
Treated for HCV			
No	517 (56.1%)	N/A	
Yes	276 (29.9%)		
Unknown	129 (14.0%)		.
Sustained viral response (after treatment)			
No	99 (35.9%)	N/A	
Yes	142 (51.5%)		
Unknown	35 (12.7%)		.
Death			
Alive	419 (45.4%)	244 (51.4%)	

Variable	Case	Controls	p-value
Death, direct LD	69 (7.5%)	8 (1.7%)	
Death, LD mentioned	60 (6.5%)	3 (0.6%)	
Death, no LD	374 (40.6%)	220 (46.3%)	<0.001

Less than half of the cases, and just over half of controls, were still alive by the end of follow up. The majority of deaths had no mention of liver disease. In controls there were 11 deaths with a mention or directly attributable to liver disease, while 69 (7.5%) of the cases had a death directly attributable to liver disease and 60 (6.5%) with a mention of liver disease.

Table 2 shows estimated HRs from complete case and imputed data for the different covariates. There is a marked increase in risk by age of transfusion, and lower risk for females. Non-UK and non-white individuals have higher risks in the univariable and complete case analyses, but this is attenuated in the imputed multivariable model. Perhaps surprisingly, there is an apparent protective effect of moderate alcohol use (<20 units/week) and little difference for higher use, compared to no alcohol. HBV shows little association.

Interestingly, the effect of being a case vs. uninfected control indicates borderline evidence of an increased hazard in the univariable analysis, no evidence of a difference for the complete case multivariable analysis, and a 20% increase in the hazard of death in the imputed multivariable model (HR=1.20, 95% CI: 1.02 to 1.41).

Table 2. Estimated hazard ratios and 95% confidence intervals for all-cause mortality according to different covariates; univariable and multivariable complete case analysis (missing observations excluded) and multivariable results based on imputed data.

	Univariable complete case	Multivariable complete case	Multivariable imputed
Age			
0-19	0.20 (0.13, 0.30)	0.13 (0.07, 0.25)	0.17 (0.11, 0.26)
20-29	0.20 (0.13, 0.30)	0.21 (0.12, 0.37)	0.21 (0.14, 0.32)
30-39	0.49 (0.35, 0.68)	0.42 (0.26, 0.68)	0.51 (0.36, 0.71)
40-49	1 (ref)	1 (ref)	1 (ref)
50-59	2.26 (1.75, 2.93)	2.31 (1.65, 3.21)	2.14 (1.65, 2.78)
60-69	3.69 (2.89, 4.71)	3.53 (2.58, 4.82)	3.50 (2.74, 4.47)
70-79	6.79 (5.09, 9.05)	6.95 (4.77, 10.14)	6.29 (4.70, 8.42)
80+	17.40 (9.60, 31.53)	19.35 (8.86, 42.23)	17.29 (9.41, 31.76)
Female	0.58 (0.50, 0.67)	0.63 (0.51, 0.78)	0.63 (0.54, 0.75)
Non-UK	0.56 (0.39, 0.80)	1.18 (0.66, 2.10)	0.97 (0.63, 1.49)
Non-white	0.36 (0.23, 0.56)	0.58 (0.26, 1.27)	0.94 (0.56, 1.60)
Alcohol			
0	1 (ref)	1 (ref)	1 (ref)
<20	0.79 (0.67, 0.95)	0.69 (0.55, 0.85)	0.69 (0.57, 0.82)
20+	1.29 (1.00, 1.67)	0.94 (0.68, 1.30)	0.92 (0.70, 1.21)
HBV	1.14 (0.70, 1.84)	1.05 (0.61, 1.81)	0.96 (0.51, 1.80)
Case vs. control	1.16 (1.00, 1.36)	1.09 (0.89, 1.33)	1.20 (1.02, 1.41)

Figure 1. Kaplan Meier survivor function for all-cause mortality in cases and controls, for four groups of age at transfusion.

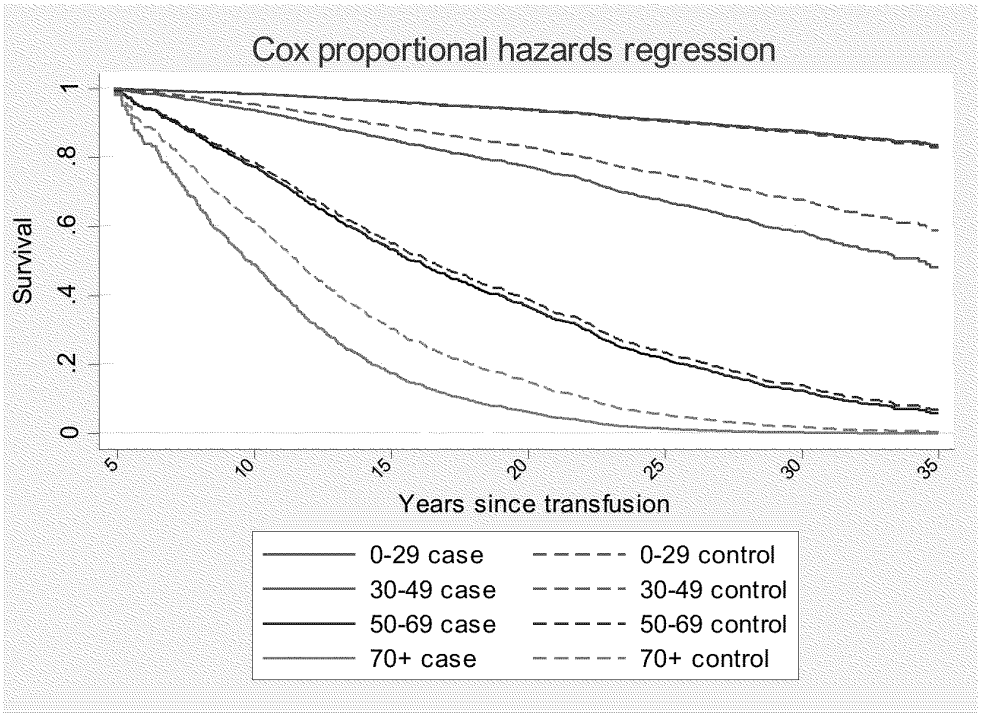

Figure 1 shows Kaplan Meier survivor functions for all-cause mortality by age at transfusion and case status; as expected the mortality approaches 100% after 30 years in the oldest ages. Survival appears slightly better in controls for the 30-49 and 70+ age groups. Including an interaction variable between 10-year age group and case/control status indicated an increased risk of cases vs. controls in the 40-49, 60-69 and 70+ age groups (HR exceeding 1.5), but little difference for other age groups. Age-specific HRs for cases vs. controls are summarised in Table 3.

Table 3. Estimated hazard ratios and 95% confidence intervals for all-cause mortality in cases vs. controls for different age groups; results from multivariable model using imputed data.

Age	HR (95% CI)
0-19	0.79 (0.38, 1.65)
20-29	1.28 (0.58, 2.81)
30-39	1.03 (0.58, 1.84)
40-49	1.76 (1.10, 2.80)
50-59	0.83 (0.58, 1.18)
60-69	1.16 (0.88, 1.52)
70-79	1.67 (1.13, 2.48)
80+	1.52 (0.46, 5.02)

Additional analyses considered the effect of baseline PCR status. In the imputed multivariable model, those testing positive at baseline had an HR of 1.53 (95% CI 1.17 to 2.00) vs. cases who tested negative, while the effect of being a negative-testing case vs. a control was HR=0.84 (95% CI: 0.64 to 1.11). In other words, those who were infected but apparently cleared the virus had no difference in hazard compared to uninfected controls.

Infected cases achieving SVR had a lower hazard than those who did not, although the analysis is misleading as individuals would have to have survived for long enough for treatments to be available; in the absence of treatment timing no sensible conclusion can be drawn.

The imputed data were used to fit competing risk models for liver disease (direct or mentioned on death certificate) with other mortality as a competing risk. Table 4 shows results from the multivariable model. Hazards increased with age, but there was no significant difference between age groups over 30. Females had a lower hazard, and non-white ethnicity a nearly 2-fold increase in hazard, although confidence intervals were wide and the result was inconclusive. Alcohol use above 20 units per week was associated with a doubling of the hazard. Finally, infected cases had substantially higher hazard ratios than uninfected controls, with an HR of 5.94 (95% CI: 3.18, 11.09).

Table 4. Hazard ratios for liver disease mortality (direct or mentioned on death certificate) with other cause of death as a competing risk.

	HR (95% CI)
Age	
0-19	0.07 (0.02, 0.25)
20-29	0.28 (0.13, 0.57)
30-39	0.63 (0.35, 1.11)
40-49	1 (ref)
50-59	0.87 (0.52, 1.44)
60-69	0.97 (0.61, 1.56)
70-79	0.52 (0.24, 1.13)
80+	N/A
Female	0.63 (0.42, 0.93)
Non-UK	0.85 (0.36, 2.03)
Non-white	1.98 (0.70, 5.54)
Alcohol	
0	1 (ref)
<20	1.00 (0.55, 1.82)
20+	2.04 (1.09, 3.81)
HBV	0.61 (0.20, 1.89)
Case	5.94 (3.18, 11.09)

Figure 2 shows cumulative incidence of liver mortality from the competing risks model, by age group and case/control status. For cases, the cumulative incidence appeared to climb more steeply in the 5-15 years after transfusion (there are no observations from 0-5 years) and level off somewhat at longer periods.

Figure 2. Cumulative incidence function of liver mortality from the Fine and Gray competing risk model, by age and infected cases vs uninfected controls.

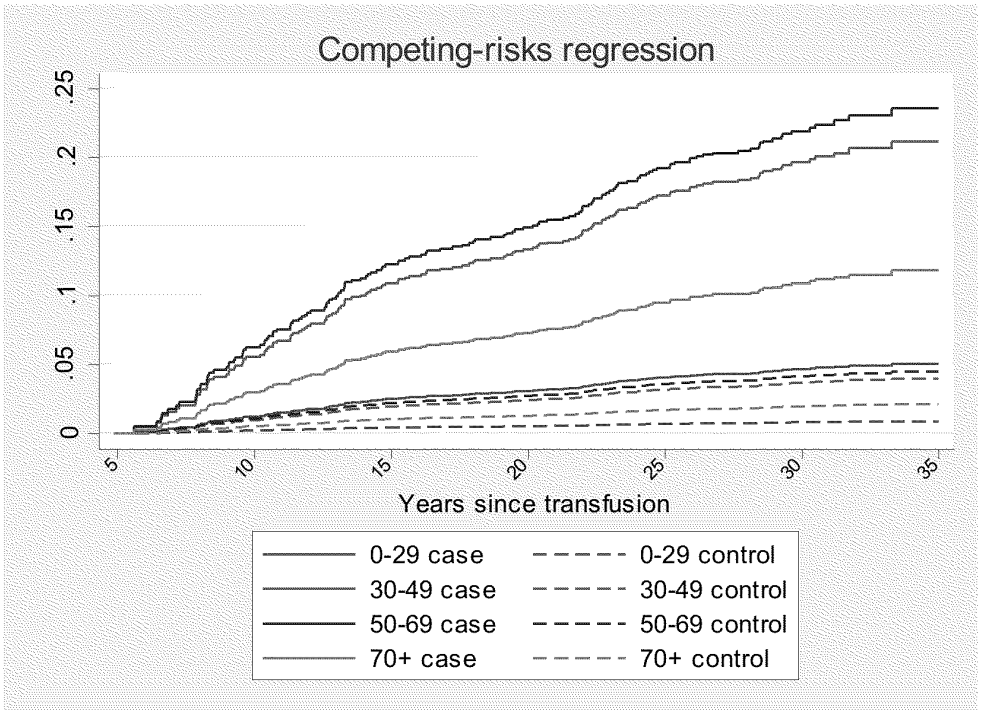

Table 4 shows estimated relative risk ratios (RRR) for cause-specific mortality by age, sex and time since transfusion case/control status. There was little evidence of a change in LD mortality outcomes by time since transfusion; deaths with LD mentioned were substantially lower in the 25+ year category, and possibly highest in the 10-15 year period, but data were fairly sparse. Risks were slightly lower for non-LD mortality after 25 years. Overall though, the model fit was similar with no time effect at all, with a reduction (improvement) in AIC score of 4.7 with the time variable omitted.

Risks of all mortality were very low in those under 30, with no LD mortality in some groups. Risks steadily increase for LD mortality from age 50 upwards, climbing to RRRs of 3-6 in the 70-79 and 80+ age groups. Non-LD mortality had a steeper gradient, with RRRs of nearly 20 in the 80+ group vs. 40-49. Females had lower risks than males for LD mortality, even less than non-LD mortality. The effect of being a case vs. an uninfected control was RRR= 4.56 (2.19, 9.49) for mortality directly attributable to LD, 10.52 (3.29, 33.60) for death with LD mentioned, and 0.95 (0.80, 1.13) for non-LD mortality.

Table 4. Estimated relative risk ratios and 95% confidence intervals for cause-specific mortality by age, sex, time since transfusion and case/control status. Results from discrete-time multinomial logit model.

	Direct LD	**LD mention**	**Non-LD**
Time since transfusion			
<10 years	0.84 (0.41, 1.74)	0.76 (0.37, 1.56)	0.69 (0.52, 0.92)

10-15 years	1 (ref)	1 (ref)	1 (ref)
15-20 years	0.65 (0.31, 1.36)	0.52 (0.24, 1.10)	0.82 (0.64, 1.04)
20-25 years	1.08 (0.55, 2.11)	0.82 (0.41, 1.63)	0.82 (0.64, 1.05)
25+ year	1.06 (0.55, 2.01)	0.28 (0.11, 0.70)	0.71 (0.55, 0.91)
Age category			
0-19	0.00 (0.00, .)	0.57 (0.07, 4.99)	0.26 (0.06, 1.08)
20-29	0.34 (0.04, 2.82)	0.00 (0.00, .)	0.83 (0.40, 1.72)
30-39	0.44 (0.09, 2.18)	0.24 (0.03, 2.10)	0.45 (0.21, 0.97)
40-49	1 (ref)	1 (ref)	1 (ref)
50-59	1.80 (0.66, 4.88)	2.39 (0.83, 6.90)	1.39 (0.83, 2.32)
60-69	3.01 (1.18, 7.67)	3.00 (1.07, 8.39)	3.33 (2.13, 5.22)
70-79	4.38 (1.78, 10.79)	3.15 (1.14, 8.76)	7.93 (5.23, 12.03)
80+	5.12 (2.00, 13.14)	6.48 (2.36, 17.79)	19.77 (13.15, 29.72)
Female vs. male	0.43 (0.27, 0.69)	0.52 (0.31, 0.88)	0.71 (0.60, 0.84)
Case vs. control	4.56 (2.19, 9.49)	10.52 (3.29, 33.60)	0.95 (0.80, 1.13)

Table 5 shows results from the same multinomial regression model as presented in Table 4, but fitted to the infected cases only. There was a somewhat greater risk of death with LD mentioned and non-LD mortality in the 10-15 years after transplant than other years. Again however, the time variable was relatively unimportant overall, with a reduction (improvement) in AIC score of 5.9 with the time variable omitted.

Table 5. Estimated relative risk ratios and 95% confidence intervals for cause-specific mortality by age, sex and time since transfusion in infected cases only. Results from discrete-time multinomial logit model.

	Direct LD	**LD mention**	**Non-LD**
Time since transfusion			
<10 years	0.76 (0.34, 1.66)	0.69 (0.33, 1.43)	0.64 (0.46, 0.90)
10-15 years	1 (ref)	1 (ref)	1 (ref)
15-20 years	0.53 (0.23, 1.23)	0.51 (0.24, 1.10)	0.66 (0.48, 0.90)
20-25 years	1.15 (0.57, 2.33)	0.71 (0.34, 1.45)	0.69 (0.50, 0.95)
25+ year	1.21 (0.62, 2.35)	0.28 (0.11, 0.71)	0.63 (0.46, 0.86)
Age category			
0-19	0.00 (0.00, .)	0.72 (0.08, 6.57)	0.42 (0.10, 1.82)
20-29	0.71 (0.07, 6.82)	0.00 (0.00, .)	0.40 (0.12, 1.37)
30-39	0.91 (0.15, 5.45)	0.30 (0.03, 2.72)	0.23 (0.07, 0.78)
40-49	1 (ref)	1 (ref)	1 (ref)
50-59	2.90 (0.78, 10.75)	2.44 (0.75, 7.97)	1.59 (0.86, 2.94)
60-69	6.07 (1.77, 20.82)	3.75 (1.22, 11.47)	3.29 (1.89, 5.72)
70-79	8.20 (2.44, 27.56)	3.93 (1.29, 11.94)	7.47 (4.46, 12.52)
80+	9.95 (2.87, 34.52)	8.30 (2.76, 24.97)	20.41 (12.31, 33.84)
Female vs. male	0.45 (0.28, 0.75)	0.54 (0.32, 0.92)	0.75 (0.60, 0.92)

Further analyses were undertaken to determine potential interaction effects. Due to the similar pattern of direct LD and LD-mentioned mortality, these outcomes were combined in a single LD outcome. Time since transfusion was also combined to 10-year intervals, and age collapsed to 4 groups, in order to increase the number of observations within each cross-classification of variables. The inclusion of interaction terms did not provide a marked improvement in model fit: compared to the model with no interaction terms, all interaction models had an increase in AIC score of at least 4.2, indicating that the additional complexity of the model was not warranted by an improvement in fit. Similarly, the model for cases only showed no substantial improvement in fit with the addition of any interaction terms.

Finally, table 6 shows predicted annual probabilities of cause-specific mortality by age and sex. After age 80, non-LD mortality was estimated at 11.7% per year overall, while LD mortality does not exceed 0.3% per year, and is less than 0.1% per year in those age less than 50.

Table 6. Predicted annual probabilities of cause-specific mortality for infected cases and uninfected controls, by age group and sex. (1) Direct liver disease (LD), (2) any mention of LD, (3) direct and mention of LD (1 and 2 combined) and (4) non-LD. Results from discrete time multinomial logit model.

	Total				Males				Females			
Age group	Direct LD	LD mention	Any LD	Non-LD	Direct LD	LD mention	Any LD	Non-LD	Direct LD	LD mention	Any LD	Non-LD
Infected cases												
0-19	0.0000	0.0014	0.0013	0.0018	0.0000	0.0017	0.0017	0.0020	0.0000	0.0009	0.0008	0.0014
20-29	0.0008	0.0000	0.0008	0.0054	0.0010	0.0000	0.0011	0.0062	0.0005	0.0000	0.0005	0.0044
30-39	0.0009	0.0005	0.0014	0.0029	0.0013	0.0007	0.0020	0.0035	0.0006	0.0003	0.0009	0.0024
40-49	0.0019	0.0017	0.0036	0.0060	0.0030	0.0025	0.0056	0.0075	0.0013	0.0013	0.0026	0.0053
50-59	0.0036	0.0038	0.0074	0.0081	0.0056	0.0056	0.0112	0.0100	0.0024	0.0028	0.0052	0.0071
60-69	0.0062	0.0054	0.0116	0.0199	0.0090	0.0075	0.0164	0.0238	0.0040	0.0037	0.0077	0.0169
70-79	0.0090	0.0060	0.0151	0.0477	0.0124	0.0079	0.0203	0.0554	0.0055	0.0040	0.0096	0.0399
80+	0.0098	0.0105	0.0202	0.1097	0.0134	0.0139	0.0273	0.1261	0.0062	0.0072	0.0133	0.0931
Uninfected controls												
0-19	0.0000	0.0001	0.0002	0.0019	0.0000	0.0002	0.0003	0.0021	0.0000	0.0001	0.0001	0.0015
20-29	0.0002	0.0000	0.0001	0.0057	0.0002	0.0000	0.0002	0.0066	0.0001	0.0000	0.0001	0.0046
30-39	0.0002	0.0000	0.0002	0.0030	0.0003	0.0001	0.0003	0.0037	0.0001	0.0000	0.0001	0.0026
40-49	0.0004	0.0002	0.0006	0.0064	0.0007	0.0002	0.0009	0.0080	0.0003	0.0001	0.0004	0.0056
50-59	0.0008	0.0004	0.0012	0.0086	0.0012	0.0005	0.0018	0.0107	0.0005	0.0003	0.0008	0.0075
60-69	0.0014	0.0005	0.0019	0.0213	0.0020	0.0007	0.0027	0.0256	0.0009	0.0004	0.0012	0.0181
70-79	0.0020	0.0006	0.0024	0.0510	0.0028	0.0007	0.0033	0.0596	0.0012	0.0004	0.0016	0.0426
80+	0.0022	0.0010	0.0032	0.1174	0.0030	0.0013	0.0045	0.1360	0.0014	0.0007	0.0021	0.0994

Conclusions

This analysis provides an update on the previous analysis of mortality in HCV-infected blood recipients and comparison with uninfected controls. Strengths include the very long follow-up time and complete ascertainment of mortality status. Some limitations of previous analyses have been addressed. These include the large amount of missing data, which has been handled via multiple imputation. Although there are potential caveats with this approach (in particular the assumption that missing values do not depend on unobserved covariate values, otherwise known as "missing at random") the approach is generally preferable to including "missing" as an additional category. Other improvements include use of the competing risks model used to better quantify mortality attributable to liver disease, and the use of a discrete-time survival model with time-varying covariates, to estimate changes in risk according to both age and time since infection.

The extended follow up and imputation approach has resulted in a modest increase (20%) in all-cause mortality risk for cases vs. uninfected controls. Further, this risk appears somewhat higher if only confirmed PCR-positive cases are considered, with PCR-negative cases having no difference in mortality to uninfected controls. The majority of covariates were not important for all-cause mortality, although females had persistently lower mortality, and there is a steep age gradient. As many individuals in this cohort were born before 1950, a great many had died by 2019.

The infected cases had substantially higher rates of liver-related mortality, with only a handful of such deaths in the controls. Ethnicity and country of birth showed little difference in the multivariable models, but females had lower risk, and higher levels of alcohol consumption were associated with higher risk. Risks of LD mortality increased markedly with age, but there was no evidence of a change in risk with time since infection. As the infected population ages an increasing proportion of individuals will develop severe liver disease and die, but it is somewhat reassuring that the infected cohort are not also accelerating towards liver disease as time since infection increases; and, the absolute risks of LD are still comparatively small in this population.

This analysis does not include up to date treatment information, which may have altered the risk of mortality in more recent years with the advent of direct-acting antivirals in 2015. Future work will aim to link individuals in this cohort to the National treatment registry, to determine precise dates of treatment, and outcome where available.