Causes of deaths among persons diagnosed with hepatitis C infection in the pre and post DAA era in England: a data linkage study

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*** Appendix**

Introduction

In the UK, while largely preventable, mortality from liver disease and liver cancer has been increasing, with the main risk factors of alcohol, obesity and viral hepatitis {Public Health England, #1477}. Around 200,000 people are chronically infected with hepatitis C virus {Public Health England, 2018 #1476} in the UK. Since the early 2000s hospital admissions within the UK from HCV-related end stage liver disease (ESLD) and hepatocellular carcinoma (HCC) have trebled, while deaths from HCV-related ESLD and HCC have more than doubled rising from 209 in 2005 to 468 in 2015 {Public Health England, 2018 #1476}. For the first time in 2016 a 3% fall in deaths from these indications was observed with provisional data suggesting a further fall of 11% in 2017 {Public Health England, 2018 #1476}.

Estimates of HCV-associated ESLD and HCC morbidity and mortality are routinely reported as national indicators rather than reporting any HCV-associated morbidity and mortality. ESLD and HCC are considered less likely to be affected by testing for and recording of HCV in admission codes in NHS Hospital Episode Statistics (HES) dataset and on death certificates collected by the Office for National Statistics (ONS). This is based on the assumption that by the time a diagnosis of ESLD or HCC is made, which is dependent on overt clinical features, the cause – e.g. HCV– will have been investigated, identified and documented in records. More consistent reporting of HCV as an associated or underlying cause is therefore expected with ESLD and HCC compared with other HCV-associated morbidities and mortality, especially if the latter are non-liver specific or asymptomatic. Therefore, because of the challenges in monitoring burden and deaths associated with HCV, little is known about all-cause mortality in those with HCV infection in England.

Robust estimates of morbidity from HCV-associated mortality for England are essential for healthcare planning, monitoring and evaluation of services. A broader analysis of HCV-associated deaths, including non-liver causes of death (e.g. overdose, suicide) will also improve our understanding of the contribution of HCV to all causes of deaths.

In this study we therefore aimed to use data linkage between sentinel surveillance of blood-borne virus testing dataset and the national death register to compare mortality between (i) those anti-HCV positive (ever HCV infected), (ii) those with a RNA positive result (current HCV infection), and (iii) the general population of England. The proportion of deaths with HCV identified as a causal or contributory factor for death were also estimated.

Methods

A retrospective descriptive analysis of linked laboratory testing data and death was undertaken.

Data sources and data linkage

Sentinel surveillance of blood borne virus testing (SSBBV) is a unique surveillance system that extracts not only positive test results, but negative tests for blood-borne viruses including anti-HCV and HCV RNA. Data collection methods for the sentinel surveillance programme have been described previously {Brant, 2008 #1342}. In summary, demographic and testing data for all individuals tested for anti-HCV and HCV RNA between January 2002 and December 2016 were extracted from 23 participating laboratory information systems in England. Individuals were de-duplicated, and test results for each individual were linked over time using a combination of soundex of surname, first initial, date of birth and NHS number. Participating laboratories are estimated to cover approximately 65% of the English population for primary and reference HCV testing and are broadly representative of most laboratories providing routine and reference HCV testing.

All persons with a positive anti-HCV test, indicative of ever being infected, or a positive RNA test, indicative of a current infection, through both diagnostic and reference testing between 2002 and 2016 were included. Persons aged <1 years were excluded due to the strong possibility of positive anti-HCV in this age group being due to persistence of maternal antibodies. Persons were linked to a data file of registered deaths provided by the Office for National Statistics (ONS), containing all causes of deaths coded using ICD10 reported for 2008 to 2016. ONS death data were linked using an unrestricted deterministic approach, using NHS Number, soundex, date of birth, sex, and initial.

Cause of death

Cause of death was obtained using the underlying cause of death reported on the death certificate, which were grouped into thirteen categories (table 1).

Table 1: Primary cause of death groupings, with ICD10 codes

Cause of death grouping	IDC10 Codes
Hepatitis	B15-19
End stage liver disease (ESLD)	I850, K704, K720, K721, K729, K767, R18
Liver cancer	C22
Alcoholic liver disease	K70, excluding K704
Non-alcoholic liver disease	K71-K77, excluding K704, K720, K721, K729, K767
HIV	B20-B24
External causes	00-Y98
Cancer (excluding liver cancer)	C00-C97, excluding C22 and C44*
Circulatory disease	I00-I99, excluding I850
Respiratory disease	J00-J99
Digestive disease (excluding hepatitis)	K00-K93, excluding K70-K77
Mental and behavioural disorders	F00-F99
Genitourinary disease	N00-N99
Other	all other ICD-10 codes

*Nonmelanoma skin cancer (NMSC) is often excluded from cancer incidence statistics because it is extremely common and registration is known to be incomplete

External causes in ICD10 includes accidents, intentional self-harm, events of undetermined intent, assault and adverse events following drugs and alcohol. In addition to the underlying cause of death up to six contributory causes can be reported for an individual, and these six contributory causes were used to estimate the proportion of deaths with HCV reported as a contributing factor.

Statistical analysis

Data were prepared in Microsoft Access, and statistical analyses were performed using STATA version 13 (Stata Corp., College Station, TX). Proportions are presented among those persons for whom the relevant information was available. Underlying cause of death, for persons dying between 2008 and 2016 were examined for persons ever- and currently-infected with HCV who tested for HCV between 2002

and 2016 and compared to the ONS causes of death for the England population during the same period. Proportions of deaths by demographic characteristics were calculated and compared using chi-squared tests. A *P* value of <0.05 was considered statistically significant.

Results

Between 2002 and 2016, 2,955,125 persons had had at least one HCV-related test reported to SSBBV, either anti-HCV or HCV RNA, of which 215,414 (7.3%) died between the period 2008 and 2016. The median age at death for all persons testing for HCV was 69 years [Interquartile range [IQR] 56-80 years], 68 years [IQR: 55-78] among men and 72 years [IQR: 58-82] among women, with men accounting for 59.7% of deaths.

Among persons with evidence of HCV infection, past or current, (defined here as either a positive anti-HCV or HCV RNA result) during the same period (204,265), 8.6% (17,588) died, with on average 2000 deaths per year, increasing from 1423 deaths in 2008 to 2647 in 2015, with a decrease to 2157 in 2016. Men accounted for 72.4% of these deaths. Median age at death for persons with evidence of HCV infection was 53 years [IQR: 44-62 years], 52 years [IQR: 44-60] among men and 54 years [44-67] among women. Compared to women, men had a higher proportion of deaths among those aged <60 years (74.3% vs. 63.9%; p <0.001).

Deaths among those with evidence of HCV infection were attributable to external causes (18.0%), circulatory causes (12.6%), cancer (excluding liver) (11.6%), liver cancer (10.1%), alcohol related liver disease (8.5%), hepatitis (8.5%), respiratory causes (7.3%), other (7.3%), non-alcohol related liver disease (4.7%), mental and behavioural (3.7%), ESLD (2.8%), digestive excluding liver (2.6%), genitourinary (1.4%) and HIV (1.0%) (figure 1). Where hepatitis was reported as the underlying cause of death (1491), 91.3% (1361) had a liver-related cause of death recorded anywhere on the death certificate. Of these, 75.7% had non-alcohol related liver disease, 50.7% had ESLD, 9.1% had alcohol related liver disease, and 7.0% had liver cancer reported.

During the study period, the proportion of deaths among those with evidence of HCV infection where the underlying cause of death was attributable to liver disease (ESLD, liver cancer, hepatitis, alcohol and non-alcohol related liver disease combined) was 34.5% (6069). However, when considering all causes of death in

those with HCV infection- regardless of the underlying cause - the proportion with any code for liver disease increases to 49.2% (8646). The number of deaths in persons with evidence of HCV where liver disease was reported anywhere on the death certificate increased 67% between 2008 and 2015, from 707 to 1184 respectively, with a 17% decrease in 2016. By liver disease cause, the biggest decrease in 2016 was in non-alcohol related liver disease (51%), followed by alcohol related liver disease (14%) and ESLD (3%). There was no difference in the number of deaths with liver cancer reported from 2015 to 2016.

Compared to deaths among the general population over the same period a significantly higher proportion of deaths among those with evidence of HCV, died of external causes (18.0% HCV positive, vs. 3.3% general population; $p<0.001$), alcohol related liver disease (8.5% vs. 0.7%; $p<0.001$), non-alcohol related liver disease (4.7%vs. 0.5%; $p<0.001$), liver cancer (10.1% vs. 0.8%; $p<0.001$), ESLD (2.8% vs. 0.3%; $p<0.001$), hepatitis (8.5% vs. 0.05%; $p<0.001$), and HIV (1.0% vs. 0.04%; $p<0.001$) (figure 1). The overall median age at death for those with evidence of HCV was 28 years younger than the median age among the general population. Table 2 shows the median age by cause of death with persons with evidence of HCV having a younger median age at death for all causes compared to the general population.

The distribution of external causes differed between persons with evidence of HCV and the general population (figure 3). Persons with evidence of HCV were more likely to die of accidental poisoning by and exposure to narcotics and psychodysleptics compared to the general population (49.7% vs. 6.0% respectively; $p<0.001$). Whereas among the general population a high proportion died of other external causes of accidental injury (29.1% vs. 60.5%; $p<0.001$), intentional self-harm (11.2% vs. 21.0%; $p<0.001$), or other (8.4% vs. 10.8%; $p<0.001$). There was no difference in the proportion who died by accidental poisoning and exposure to alcohol (1.7% vs. 1.8%; $p=0.656$) between persons with evidence of HCV and the general population.

Of the 17,588 persons with evidence of HCV (either a positive anti-HCV or HCV RNA), 15,141 (86.1%) had an RNA result, for which the last reported RNA was negative for

4329 (28.6%). A significantly higher proportion of persons where their last reported RNA was negative died of circulatory causes (14.6% vs. 11.1%; p<0.001), external causes (20.9% vs. 16.6%; p<0.001), genitourinary causes (1.7% vs. 1.3%; p=0.024), cancer (excluding liver) (14.3% vs 10.0%; p<0.001), other causes (8.1% vs. 7.0%; p=0.017) and respiratory causes (8.7% vs. 6.3%; p<0.001) compared to persons where their last reported RNA was positive. Conversely, persons where their last reported RNA was positive had a significantly higher proportion of deaths with hepatitis causes (4.7% vs. 11.1%; p<0.001), non-alcohol related liver disease (7.9% vs. 9.0%; p<0.001) and liver cancer (5.0% vs. 12.5%; p<0.001) (figure 2).

HCV was recorded as a contributing cause of death for 28.4% (4994/17,588) of those with evidence of HCV (either anti-HCV or HCV RNA positive). Among these persons who died of liver disease (figure 4), the proportion of deaths among persons with evidence of HCV for which HCV was reported as a contributing factor was 58.8%. Broken down by liver disease cause, these proportions were, 46.2% for alcohol related liver disease, 40.2% for end stage liver disease, 59.8% for liver cancer, and 18.3% for non-alcohol related liver cancer.

Discussion

Our findings indicated that 8.6% of persons in SSBBV with evidence of past or current HCV infection, (either anti-HCV or HCV RNA positive), died between 2008 and 2016. The most common underlying cause of death was external causes, in particular accidental overdose by and exposure to narcotics (opioids, synthetic and unspecified narcotics, derivatives) and psychodysleptics (hallucinogens), which is consistent with the UK epidemiology of HCV where persons at greatest risk of HCV are people who are current or past injecting drug users.

Half of persons with evidence of HCV who had died during this period had liver disease (ESLD, liver cancer, hepatitis, alcohol and/or non-alcohol related liver disease) reported as a cause of death anywhere on their death certificate, which reflects the natural history of HCV infection and frequency of co-morbidity with alcohol. It is important to note that the proportion of individuals with liver disease reported anywhere on their death certificate (49%) was higher than liver disease reported as underlying cause of death (35%); this difference was due to individuals who had HCV reported as the underlying cause of death and liver disease reported as an associated cause of death. In line with the highest prevalence of HCV in the UK being in people who inject drugs (PWID), compared with the general population, those with evidence of HCV infection had a higher proportion of persons dying of liver related and external causes related to narcotics poisoning, and had a markedly lower median age of death.

The median age at death among those with evidence of HCV infection is lower than in the general population overall and by cause of death, consistent with previous studies {Mahajan, 2014 #1378;Omland, 2011 #1464}. The demographic distribution of those with evidence of HCV infection reported to have died has similarities with the demographics of those testing and at risk for HCV, with a higher proportion of deaths among men {Public Health England, 2016 #1344}, and a high proportion of persons dying due to drug misuse. Furthermore it is well documented that the rate of disease progression of HCV is lower in women {Westbrook, 2014 #1454}, and while potentially confounded by many other factors such as age at acquisition of

infection, other co-morbidities, alcohol and smoking, this is likely reflected in the proportion of women dying compared with men, and the disparities in the age of death between men and women in our analysis.

A further key finding is that following an overall increase in deaths with liver disease reported anywhere on the death certificate over the past years, a decrease of17% was observed for the first time in 2016. A decrease of 11% was observed in HCV-associated ESLD death registrations using ONS (unlinked) data. This fall in deaths may be associated with the introduction and scale up of DAAs which became widely available on the NHS from 2015, are injection-free, easier to tolerate, of shorter treatment duration, and have a much higher success rate in terms of virus clearance (as measured by sustained virological response, SVR) compared to the previous standards of care (ref for SVR –from HCV report or BVHGguidance). It was anticipated that these DAAs would transform the treatment landscape, and improve treatment uptake, completion and success, and contribute to the UK's attainment of the WHO goal of eliminating hepatitis C as a major public health threat by 2030. Our data provide baseline and encouraging early impact data of new treatment regimens on HCV associated all cause liver mortality.

However, while there were decreases in the reporting of HCV-associated ESLD deaths, alcohol related and non-alcohol related liver disease, there was no difference in the number of persons with liver cancer reported on their death certificate. This was also seen in death registration data from ONS where HCV-related HCC (liver cancer) continued to rise {Public Health England, 2018 #1476}. This suggests that while DAA drugs may lead to a reduction in deaths from liver disease, the risk of death from liver cancer may persist even after successful clearance of the virus, particularly amongst those with pre-existing co-factors for liver disease, because their liver disease is at a more advanced stage with precancerous lesions when treated, having been infected for more years. From a clinical care perspective, this highlights the importance of ongoing surveillance for HCC in those who clear the virus (ref from hcv uk report). The poor overall prognosis of liver cancer may also be a contributory factor, noting that in England only 36% of persons survive with liver

cancer for one year or more post cancer diagnosis and that emergency presentation is the most common route of diagnosis for liver cancer within the UK, with much lower survival rates compared to being diagnosed earlier {National Cancer Intellegence Network, 2014 #1278}. These data are therefore supportive of early HCV treatment to achieve better patient outcomes.

The finding that external causes of death, defined as suicide, accidental or drug-related, were more likely in persons with evidence of HCV than among the general population is consistent with other studies. A study following a cohort of patients with serum stored between 1971 and 1975 identified that those anti-HCV positive were eight times more likely to die from suicide or drug overdose than from HCV-associated disease {Rodger, 2000 #1478}. Furthermore, drug use and drug dependence are known causes of premature mortality, and is associated with alcohol use, with a third of persons in drug treatment mentioning alcohol use {Public Health England, 2014 #1479}. Our study also showed an additional contribution of HCV to the lower median age of death already observed in persons who died of external causes. Sub-categories of external causes indicated that those with hepatitis had a higher proportion of external deaths due to accidental poisoning by exposure to narcotics and psychodysleptic compared to the general population. The association between suicides, accidental or drug related deaths and HCV has been previously documented {Dragisic, 2015 #1448;Maloney, 2007 #1449;Darke, 2005 #1450;Darke, 2002 #1451;Conner, 2003 #1452}.

Interestingly, external causes were still one of the main causes of death among persons with evidence of HCV or a negative RNA result reported and significantly higher compared with those who continued to be RNA positive. The high proportion of external causes of death regardless of RNA status reflects the major contribution of high risk behaviours among PWIDs (e.g. overdose), likely independent of liver disease and HCV viraemic status, and highlights the need to ensure that a broad range of patient-focused addiction services including drug services, mental health, social services, need to be maintained alongside HCV prevention and treatment services. The relative proportion of all other causes of deaths among persons RNA

negative compared to RNA positive were more aligned with that observed in the general population with higher proportion of deaths due to circulatory, respiratory, genitourinary, other causes and cancers excluding liver. This would support the hypothesis that there is a reduction in liver disease mortality risk towards general population levels once HCV infection is cleared but this needs further investigation of mortality rates in HCV RNA positive and negative populations.

Also of note is the relatively high proportion of persons where their underlying cause of death was reported as HIV. This proportion is likely to be an underestimate as we have only included the underlying cause of death for an individual, and have not considered AIDS defining illnesses as a flag for HIV mortality. The rate of co-infection is important to quantify as it is associated with faster disease progression rates for both infections {Graham, 2001 #1456;Benhamou, 1999 #1457;Greub, 2000 #1458;Chen, 2009 #1459;Rockstroh, 2005 #1460}. Recent estimates of co-infection in tested populations (also using data linkage with SSBBV) suggests 5.0% of persons with HCV are co-infected with HIV {Ireland, 2018 #1480}, with a higher proportion of persons with HIV estimated to be co-infected with HCV (ranging from 4.1-9.9%) {Price, 2013 #1461;Thornton, 2015 #1462}.

These linked data provide an opportunity to estimate more confidently HCV-associated mortality and highlights under-diagnosis, variable and under-reporting of HCV-associated deaths in death registers. We estimated that one in three persons had an underlying cause of death attributable to liver-related causes, increasing to one in two if all causes reported on the death certificate were considered. Our findings also indicated that reporting of HCV-associated deaths using death registers could be as low as 29% overall, with liver related causes much more completely reported at 44%-60%. This is consistent with published literature, Mahajan et al, indicated that within four US healthcare systems between 2006-2010 only 19% deaths amongst persons with HCV had HCV indicated on their death certificate, with 41% of those dying of liver related causes, and 31% among those dying of liver cancer {Mahajan, 2014 #1277}. By contrast, in Scotland between 1991 and 2006, HCV was mentioned on the death certificate for 52% of persons anti-HCV positive

who died of liver-related causes (51% between 1991 and 1999, and 52% between 2000 and 2006); this higher proportion is likely attributable to routine record linkage between an HCV diagnosis database and the death register in Scotland, reducing effects of underascertainment {McDonald, 2010 #1386}. Underreporting the HCV-associated liver mortality has implications for modeling the past and future prevalence and burden of disease from HCV but can be adjusted for if the magnitude of underreporting is estimated and non-random biases in underreporting are not at play.

There are several limitations worthy of discussion. Firstly, data collected by SSBBV lacks additional information on risk factors so confounders could not be adjusted for. Secondly, the data used are derived from a sentinel network of laboratories, which cover approximately 40% of England's GP population, with coverage varying by area (PHE region). As a result, SSBBV does not collect all test data in England and subsequent positive or negative RNA tests may be missing if done outside the SSBBV network. Further RNA tests may also be missing as the test was not requested, however, overall the proportion without an RNA test was low at 13.9% . Thirdly, the data are right and left censored, as only those tested and who died in the defined time periods are included, which mainly excludes those tested between 1996 and 2002 and died before 2008. However, the study periods allow for a more contemporaneous and therefore relevant exploration of causes of death, and were chosen to maximise potential for matching and reduce biases introduced through incomplete linking identifiers and inconsistent laboratory reporting before mandatory reporting was introduced mid-2000s.

In summary, by linking HCV testing data from SSBBV with registered deaths from ONS during the period of our study, we found that compared to the general population, a higher proportion of deaths among those with evidence of HCV in a tested population dataset were liver-related and external causes, in particular accidental poisoning by and exposure to narcotics and psychodysleptics. While circulatory and respiratory causes of death contributed a considerable proportion of deaths in those with evidence of HCV infection in the test dataset, their relative

contribution was much lower among HCV infected persons compared to the general population, except in a sub-population of tested persons who had evidence of clearing HCV infection. We estimate that 8.6% of persons with evidence of HCV died between 2008 and 2016, with the majority of persons dying prematurely.

With improved access to more effective DAA, a decrease in mortality from HCV associated ESLD has been observed {Public Health England, 2017 #1376}. Our data corroborate this 3% decline in HCV-associated ESLD deaths seen in 2016 compared to 2015, and further suggest reductions in the contribution of other liver disease causes (excluding cancer) to deaths in persons with evidence of HCV. This early evidence of impact of DAA on liver related mortality is important to monitor to see if it is sustained, and to see if any impact on HCV-related liver cancer deaths materialises. Moreover, changes in HCV associated liver disease and cancer mortality may be a useful additional metric for monitoring impact of HCV treatment coverage and other control interventions on premature mortality from liver disease and cancer –both national targets {PHOF- https://fingertips.phe.org.uk/profile/public-health-outcomes-framework}. In addition, impact of control efforts, if any, on non–liver related causes of deaths such as from illicit drug use can also be monitored through this data linkage approach, noting that there is some evidence that HCV treatment and cure may be associated with recovery from addiction and therefore could potentially reduce drug -associated deaths {PHE; Health matters: preventing drug misuse death}. Data linkage to describe HCV-related mortality therefore gives us a more complete understanding of the causes of death in those diagnosed with HCV and can help with accounting for underreporting of HCV in death and, indeed, other routine data sources such as hospital episode statistics. This will allow us to monitor and more confidently interpret changes in mortality patterns as interventions are ramped up to achieve the WHO global HCV elimination goal {World Health Organisation, 2016 #1463}.

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References

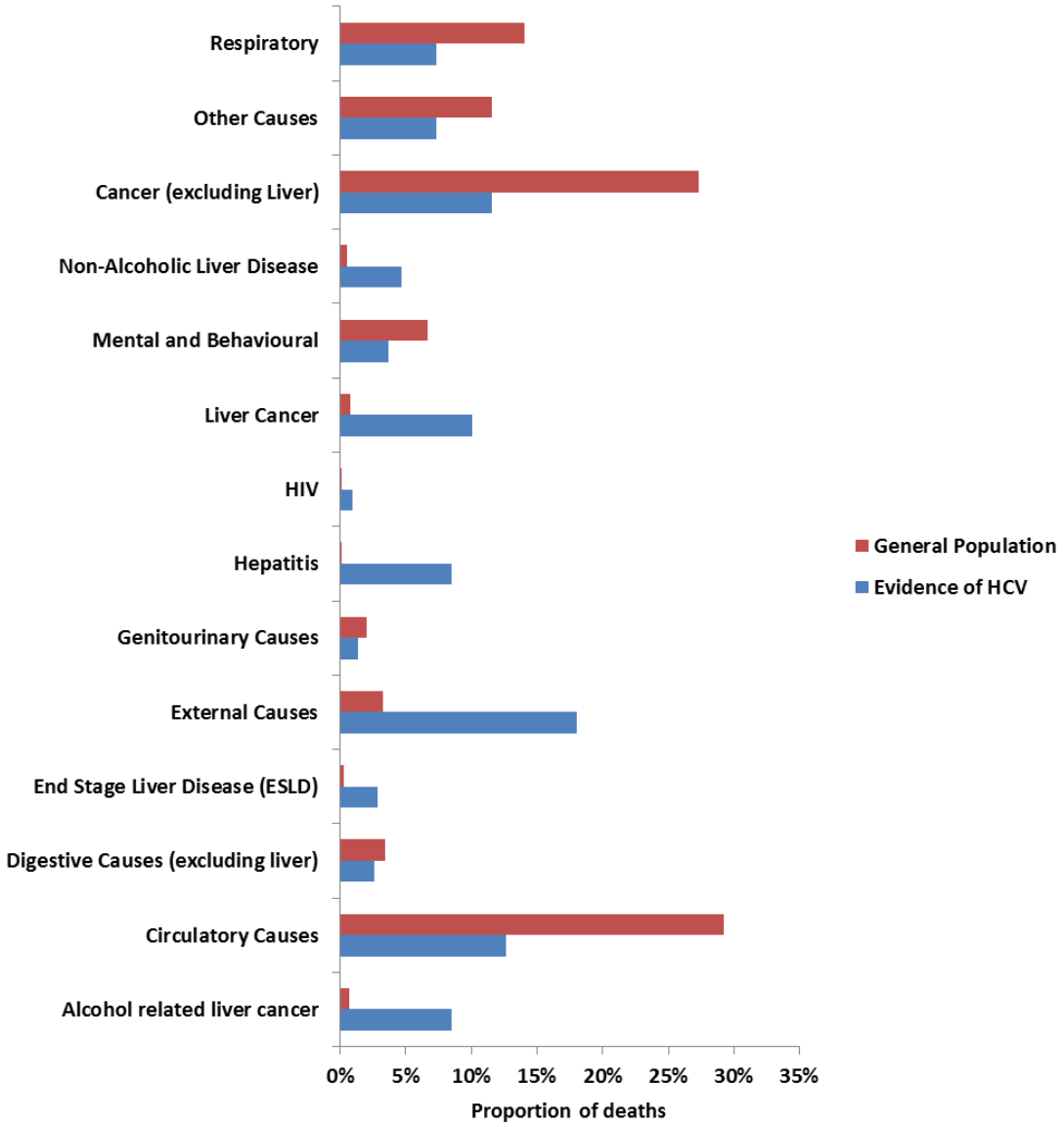


Figure 1: All-cause mortality (underlying cause) by the general population and individuals with evidence of HCV from tested population in SSBBV, England 2008-2016 .

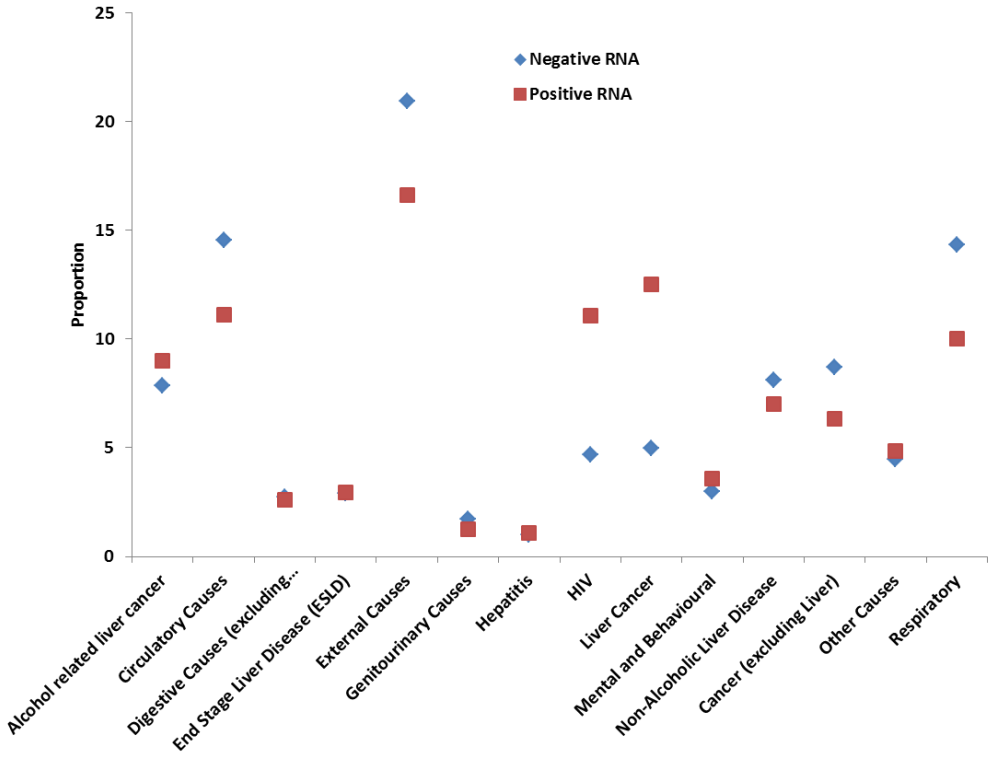


Figure 2: All-cause mortality (underlying cause) by final HCV RNA status following an anti-HCV positive result, England 2008-2016.

	General Population		Evidence of HCV	
	Median age at death	(IQR)	Median age at death	(IQR)
All-causes	81	(71-88	53	(44-62)
Alcohol related liver cancer	55	(47-63)	48	(42-54)
Circulatory Causes	83	(74-89)	57	(47-69)
Digestive Causes (excluding liver)	82	(74-88)	54	(47-64)
End Stage Liver Disease (ESLD)	57	(48-66)	50	(43-49)
External Causes	64	(42-84)	43	(37-49)
Genitourinary Causes	86	(80-91)	69	(38-51)
Hepatitis	58	(50-67)	57	(49-65)
HIV	47	(40-57)	45	(38-51)
Liver Cancer	74	(65-82)	60	(55-68)
Mental and Behavioural	88	(83-92)	52	(36-52)
Non-Alcoholic Liver Disease	67	(56-77)	52	(46-60)
Cancer (excluding Liver)	83	(74-89)	58	(51-66)
Other Causes	84	(73-90)	52	(43-64)
Respiratory	84	(76-89)	56	(48-66)

Table 1: Median age at death for persons with evidence of HCV and the general population by cause of death, 2008-2016.

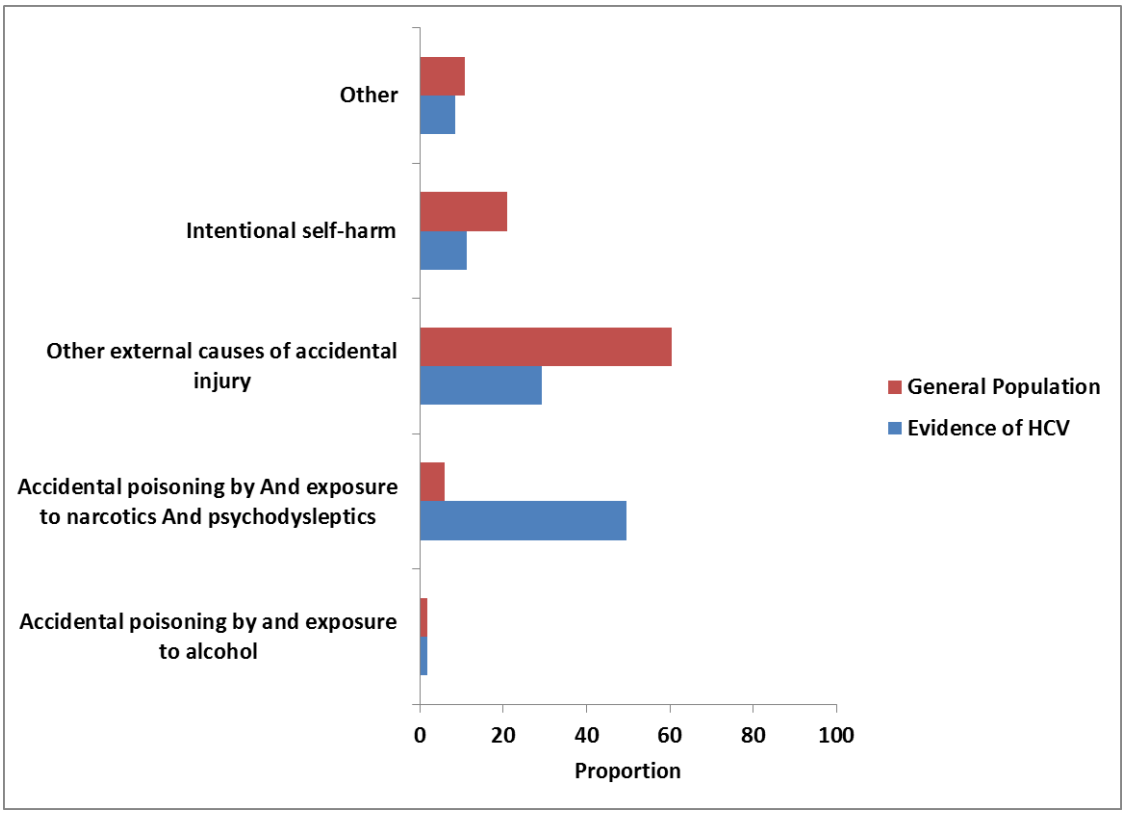
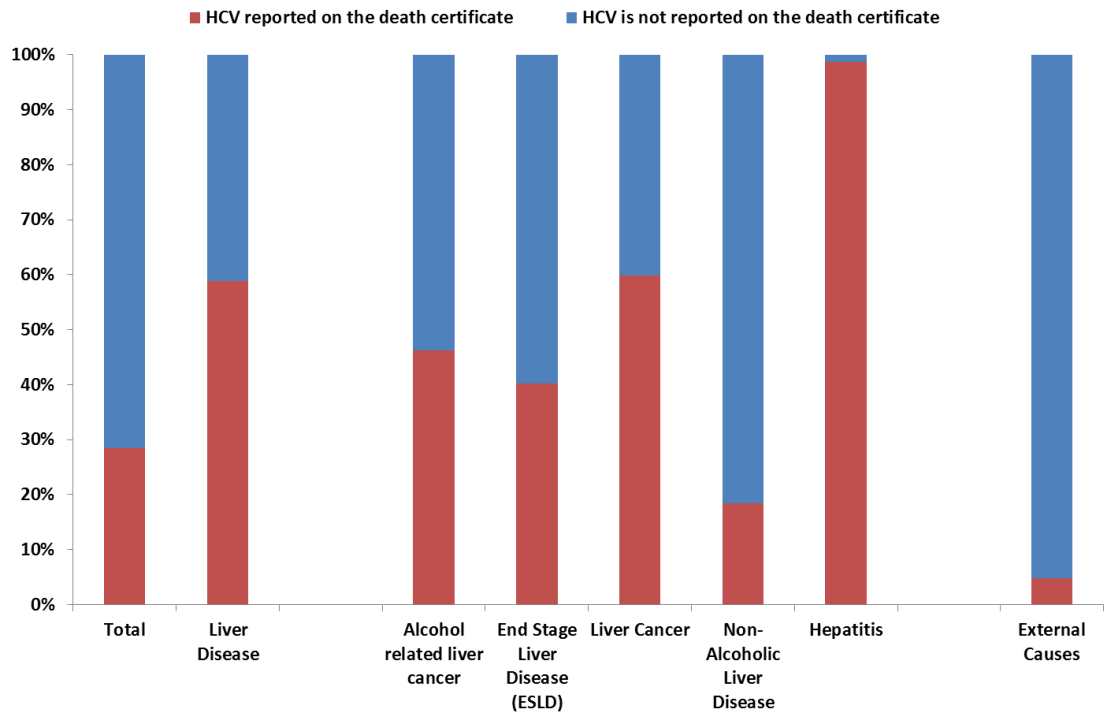


Figure 3: External causes by the general population and evidence of HCV, England 2008-2016.



* Liver disease includes alcohol related liver cancer, end stage liver cancer, liver cancer, non-alcohol related liver cancer, and hepatitis. External causes includes accidents, intentional self-harm, events of undetermined intent, assault and adverse events following drugs.

Figure 4: All causes of death with HCV listed as a contributing cause of death among those with evidence of HCV.