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Viral Hepatitis

Mortality in hepatitis C patients who achieve a sustained viral response compared to the general population

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Background & Aims: The number of people living with previous hepatitis C infection that have attained a sustained viral response (SVR) is expected to grow rapidly. So far, the prognosis of this group relative to the general population is unclear.

Methods: Individuals attaining SVR in Scotland in 1996–2011 were identified using a national database. Through record-linkage, we obtained cause-specific mortality data complete to Dec 2013. We calculated standardised mortality ratios (SMRs) to compare the frequency of mortality in SVR patients to the general population. In a parallel analysis, we used Cox regression to identify modifiable patient characteristics associated with post-SVR mortality.

Results: We identified 1824 patients, followed on average for 5.2 years after SVR. In total, 78 deaths were observed. Overall, all-cause mortality was 1.9 times more frequent for SVR patients than the general population (SMR: 1.86; 95% confidence interval (CI): 1.49–2.32). Significant cause-specific elevations were seen for death due to primary liver cancer (SMR: 23.50; 95% CI: 12.23–45.16), and death due to drug-related causes (SMR: 6.58, 95% CI: 4.15–10.45). Together these two causes accounted for 66% of the total excess death observed. All of the modifiable characteristics associated with increased mortality were markers either of heavy alcohol use or injecting drug use. Individuals without these behavioural markers (32.8% of cohort) experienced equivalent survival to the general population (SMR: 0.70; 95% CI: 0.41–1.18)

Conclusions: Mortality in Scottish SVR patients is higher overall than the general population. The excess was driven by death from drug-related causes and liver cancer. Health risk behaviours emerged as important modifiable determinants of mortality in this population.

Lay summary: Patients cured of hepatitis C through treatment had a higher mortality rate overall than the general population. Most of the surplus mortality was due to drug-related causes and death from liver cancer. A history of heavy alcohol and injecting drug use were associated with a higher mortality risk.

Introduction

The use of direct-acting antiviral drugs has led to vast improvements in the efficacy and tolerability of treatment for chronic hepatitis C virus (HCV) infection [1,2]. As a result, the number of previously-infected persons living with a sustained viral response (SVR) is likely to increase rapidly in the years ahead. It is important therefore to gain a better understanding of what an SVR means in terms of an individual's subsequent health. SVR is regarded as a "cure" by clinicians [3], patients [4], pharmaceutical companies [5,6], and the lay media [7]. Whilst this is accurate in virological terms (i.e., SVR *does* represent a durable eradication of the virus from blood serum [8]), the extent to which SVR is a cure for other noted aspects of the hepatitis C condition – namely: liver fibrosis [9], hepatocellular carcinoma [10], increased all-cause mortality relative to the general population [11] and extrahepatic manifestations [12] – remains unclear. The object of this study was to evaluate the mortality rate aspect of this knowledge gap. Although we know that SVR patients have lower mortality rates than non-SVR patients [3,13] we do not know how the mortality of this group compares to the general population. This is in contrast with other fields of medicine, such as oncology, where comparing patient survival against the general population is central to determining rates of cure [14,15].

Thus far, only two studies have compared mortality in SVR patients to the general population. The first study was based on

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192 SVR patients recruited from five tertiary liver clinics in Europe and Canada [16]. All patients had advanced fibrosis at baseline and the average age was 49 years. For this cohort, ten-year survival – at 91.1% – was no different to survival in the general population. More recently, Bruno *et al.* examined survival in 181 SVR patients recruited from five clinics in Italy [17]. All individuals in this cohort had compensated cirrhosis at baseline, and the average age was 59 years. Here too, ten-year survival – at 90.9% – was comparable to the general population. These initial data are encouraging, nevertheless a question mark remains over how representative their findings are to the wider SVR population. Firstly, because both studies were confined to patients with advanced fibrosis and did not include patients with milder disease (i.e., the group where the greatest burden of infection lies [18]). Secondly, because patients in both studies were recruited from potentially select clinics that may not be representative – either in terms of the patient case mix or the clinical care received – of all clinics administering therapy. Therefore, in this study we analysed mortality data from a large nationwide cohort of SVR patients in Scotland. Our objective was to compare cause-specific mortality in SVR patients to the underlying general population.

Patients and methods

Data sources

Data on cause-specific mortality rates in SVR patients
We used data from a previously-described [19] retrospective cohort of HCV infected patients treated in Scotland who began and terminated a course of interferon (IFN)-based antiviral therapy between Jan 1996 and Dec 2010, respectively. This cohort was restricted to patients who were treatment-naïve, and who at the time of treatment, had compensated liver disease. It further excluded individuals with HIV or hepatitis B co-infection (the latter was inferred on the basis of surface antigen positivity). In total, 3385 individuals met these criteria of whom 1824 attained SVR and form the focus of this present analysis. Subsequent mortality data, specifically information on the date and the cause of death, were obtained through record-linkage to the Scottish mortality register (see [16] for further details). We examined the following seven causes of death; death due to: (i) primary liver cancer, (ii) other liver disease (i.e., liver death not due to primary liver cancer), (iii) drug-related causes, (iv) external causes (referring mainly to death from accidents, homicide, and suicide), (v) all non-liver cancers, (vi) diseases of the circulatory system, (vii) and all other causes not listed above. We used the international classification of disease (ICD) code present in the underlying cause of death field to define these mortality categories (Supplementary Table 1). Mortality rates were expressed in terms of person-years of follow-up. For each individual, we commenced follow-up at 9 months after antiviral treatment was stopped (thereby factoring in 6 months for SVR eligibility and a further 3-month grace period to physically receive the requisite SVR test), and ended follow-up at the date of mortality, or the date that our extract of the mortality register was complete until (31 Dec 2013).

Data on cause-specific mortality rates in the general population
We obtained a bespoke dataset from the General Registry Office Scotland of all deaths occurring in Scotland between 1996 and 2014, according to the underlying cause of death, the age at death, the calendar year of death, and the decedent's gender. We linked this dataset to mid-year Scottish population estimates to determine cause-specific mortality rates for the general population. We examined the same seven causes of death as for our SVR cohort and again used the ICD code present in the underlying cause of death field to define these categories (Supplementary Table 1).

Statistical analysis

Survival in SVR patients relative to the general population
Ten-year survival function. We calculated the Kaplan-Meier survival function up to ten years after SVR, and juxtaposed this against the survival function for the general population according to the equivalent age, sex and calendar year distribution. We generated these curves both in relation to the total cohort (N = 1824), and also specifically for SVR patients who had not received a diagnosis of cirrhosis at baseline (N = 1717). Our rationale for focusing on this latter subgroup was that non-cirrhotic SVR patients tend to be discharged from clinical care and their liver-related mortality should be low.

Standardised mortality ratios. The standardised mortality ratios (SMR) represents the ratio of the number of expected deaths (i.e., expected given general population mortality rates) to the number of *observed* deaths. We determined the standardised mortality ratio (SMR) adjusted for age, gender and calendar year. We calculated the SMR for all-cause mortality, as well as the SMR for each of the seven causes of death listed afore. As per our estimates of ten-year survival, SMRs were determined both for all SVR patients, and also specifically for SVR patients who had not received a diagnosis of cirrhosis at baseline.

Identifying baseline factors associated with post-SVR mortality
We used Cox regression to identify baseline patient characteristics associated with post-SVR mortality. The baseline factors we assessed were: (i) age group (<35 years; 35–49 years; and >50 years); (ii) gender; (iii) diagnosis of liver cirrhosis; (iv) Charlson comorbidity index (CCI); (v) genotype; (vi) maximum alcohol consumption sustained for at least six months; (vii) intravenous drug use history; (viii) past hospitalisation for alcohol intoxication; (ix) past hospitalisation for violence-related injury; (x) past hospitalisation for drug intoxication; (xi) pre-treatment aspartate aminotransferase-to-platelet-ratio index (APRI); and (xii) pre-treatment gamma glutamyl transferase(GGT). Diagnosed liver cirrhosis refers to whether the patient had been diagnosed with liver cirrhosis by the time of SVR attainment. Diagnosis of liver cirrhosis in Scotland over this study period was made through a combination of biopsy; transient elastography; abdominal ultrasound; clinical examination; and routine liver function tests. Intravenous drug use history and maximum alcohol consumption were determined from data self-reported by the patient at the time of their liver clinic assessment. Maximum alcohol consumption was specifically defined as the highest level of alcohol use, sustained for six months or more, prior to being seen at the HCV treatment clinic. This was categorised as <21 units/week; 22–49 units/week and $\geqslant$50 units/week. Past hospitalisation for alcohol intoxication, violence-related injury and drug intoxication were determined from historical hospitalisation records dating back to Jan 1980. The ICD codes used to define these events are listed in Supplementary Table 2. We calculated the CCI to gauge each patients' comorbidity burden at baseline [20]. The CCI assigns a score of 1–6 for each comorbidity present, with a higher score denoting greater severity: A metastatic solid tumour, for example, carries a score of 6, renal disease carries a score of 2, whereas uncomplicated diabetes incurs a score of 1. The final CCI for an individual is the total of these scores. We used historical hospitalisation data dating back to January 1, 1980 to determine the presence/absence of the various comorbidities at baseline (as per the ICD codes set out by Quan *et al.* [21]). We extracted all liver function tests recorded on the clinical database within 2 years of starting treatment. We calculated the mean aspartate aminotransferase level and mean platelet count in order to infer the APRI. We categorised APRI as <0.7 and $\geqslant$0.7 corresponding to the optimal cut off to distinguish individuals with mild fibrosis (i.e., Metavir F0–F1) from individuals with non-mild fibrosis (i.e., Metavir F2+) [22]. We further determined the mean level of GGT, given that this was previously found to be an important determinant of SVR attainment in Scotland [23]. Associations between these 12 baseline factors and all-cause mortality were calculated initially both in their crude unadjusted forms, and after adjustment for age group, gender, cirrhosis and CCI. As with our SMR analysis, associations were calculated separately both for all SVR patients, as well as specifically for SVR patients without a diagnosis of cirrhosis at baseline.

Results

Description of the SVR patients at baseline

In this cohort of 1824 SVR patients, the mean age was 40.7 years and most individuals were male (67.9%; Table 1). The median calendar period at baseline was 2008 (interquartile range: 2006–2010). All patients had compensated liver disease. Liver cirrhosis was diagnosed in 5.8%, and 53.6% had an APRI score <0.7 (indicative of Metavir F0–F1) where this score was known. In terms of health risk behaviours, almost a fifth (18.1%) had a history of heavy alcohol use, and 58.6% reported ever injecting drugs.

Table 1. Baseline characteristics associated with post-SVR mortality for: (i) all SVR patients; and (ii) SVR patients without cirrhosis at baseline.

Category	Variable		(I) All SVR patients; (n = 1824)				(ii) SVR patients without baseline cirrhosis; (n = 1717)			
			Number (col %)	Deaths	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[†]	Number (col %)	Deaths	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[‡]
Basic demographics	(i) Age group	<35 yr	542 (29.7)	11	Ref. (1.00)	Ref. (1.00)	538 (31.3)	11	Ref. (1.00)	Ref. (1.00)
		35-49 yr	976 (53.5)	41	2.14 (1.10-4.16)*	1.79 (0.91-3.54)	922 (53.7)	33	1.82 (0.92-3.61)	1.73 (0.87-3.46)
		50 +yr	306 (16.8)	26	4.28 (2.11-8.68)***	2.76 (1.31-5.84)**	257 (15.0)	14	2.74 (1.24-6.06)*	2.55 (1.15-5.69)*
	(ii) Gender	Female	585 (32.1)	12	Ref. (1.00)	Ref. (1.00)	556 (32.4)	10	Ref. (1.00)	Ref. (1.00)
		Male	1239 (67.9)	66	2.75 (1.49-5.09)**	2.58 (1.39-4.79)**	1161 (67.6)	48	2.45 (1.24-4.85)*	2.44 (1.23-4.82)*
Medical co-morbidities	(iii) Diagnosed with cirrhosis	No	1717 (94.1)	58	Ref. (1.00)	Ref. (1.00)	1717 (100.0)	58	\	\
		Yes	107 (5.9)	20	5.34 (3.21-8.89)***	3.11 (1.72-5.60)***	0 (0.0)	0	\	\
	(iv) Charlson co-morbidity index	None (0)	993 (54.4)	30	Ref. (1.00)	Ref. (1.00)	966 (56.3)	27	Ref. (1.00)	Ref. (1.00)
		Medium (1-2)	758 (41.6)	35	1.04 (0.64-1.72)	0.87 (0.53-1.45)	704 (41.0)	26	0.92 (0.53-1.60)	0.85 (0.49-1.48)
		High (3+)	73 (4.0)	13	5.27 (2.75-10.13)***	2.35 (1.13-4.90)*	47 (2.7)	5	3.33 (1.28-8.68)*	2.84 (1.08-7.45)*
Viral genotype	(v) Genotype	Non-3	612 (33.6)	27	Ref. (1.00)	Ref. (1.00)	582 (33.9)	22	Ref. (1.00)	Ref. (1.00)
		3	1130 (62.0)	44	0.80 (0.50-1.30)	0.77 (0.47-1.25)	1057 (61.6)	30	0.69 (0.40-1.20)	0.73 (0.42-1.28)
		Missing	82 (4.5)	7	0.88 (0.37-2.10)	0.99 (0.41-2.37)	78 (4.5)	6	0.97 (0.38-2.50)	1.04 (0.40-2.67)
Health risk behaviours	(vi) Maximum units/wk alcohol sustained for at least six months	<21	1378 (75.6)	45	Ref. (1.00)	Ref. (1.00)	1321 (76.9)	39	Ref. (1.00)	Ref. (1.00)
		22-49	116 (6.4)	4	0.93 (0.33-2.58)	0.66 (0.23-1.86)	107 (6.2)	2	0.57 (0.14-2.35)	0.49 (0.12-2.06)
		50+	330 (18.1)	29	3.02 (1.89-4.82)***	2.12 (1.30-3.47)**	289 (16.8)	17	2.25 (1.27-3.99)**	1.91 (1.07-3.43)*
	(vii) History of intravenous drug use	No	756 (41.5)	25	Ref. (1.00)	Ref. (1.00)	703 (40.9)	12	Ref. (1.00)	Ref. (1.00)
		Yes	1068 (58.6)	53	1.75 (1.09-2.82)*	2.36 (1.41-3.94)**	1014 (59.1)	46	3.14 (1.66-5.94)***	3.41 (1.77-6.56)***
	(viii) Past hospitalisation for alcohol intoxication	No	1699 (93.2)	65	Ref. (1.00)	Ref. (1.00)	1604 (93.4)	48	Ref. (1.00)	Ref. (1.00)
		Yes	125 (6.9)	13	3.25 (1.79-5.90)***	3.17 (1.72-5.85)***	113 (6.6)	10	3.49 (1.76-6.91)***	3.42 (1.71-6.82)***
	(viiii) Past hospitalisation for violence-related injury	No	1503 (82.4)	58	Ref. (1.00)	Ref. (1.00)	1415 (82.4)	43	Ref. (1.00)	Ref. (1.00)
		Yes	321 (17.6)	20	2.01 (1.21-3.35)**	1.88 (1.10-3.20)*	302 (17.6)	15	2.05 (1.14-3.71)*	1.84 (1.00-3.40)*
	(x) Past hospitalisation for drug intoxication	No	1563 (85.7)	58	Ref. (1.00)	Ref. (1.00)	1468 (85.5)	39	Ref.(1.00)	Ref. (1.00)
		Yes	261 (14.3)	20	2.34 (1.41-3.90)**	2.87 (1.68-4.89)***	249 (14.5)	19	3.26 (1.88-5.65)***	3.59 (2.01-6.41)***
Liver function tests	(xi) Mean AST-to-platelet ratio-index	<0.7 (~mild fibrosis)	639 (35.0)	24	Ref. (1.00)	Ref. (1.00)	632 (36.8)	22	Ref. (1.00)	Ref. (1.00)
		≥0.7 (~ non-mild fibrosis)	553 (30.3)	21	0.85 (0.47-1.52)	0.50 (0.27-0.94)*	496 (28.9)	12	0.58 (0.29-1.18)	0.51 (0.25-1.03)*
		Missing	632 (34.7)	33	1.11 (0.66-1.89)	0.76 (0.43-1.32)	589 (34.3)	24	0.96 (0.53-1.71)	0.87 (0.48-1.57)
	(xii) Mean GGT before treatment (IU/L)	<55	933 (51.2)	26	Ref. (1.00)	Ref. (1.00)	913 (53.2)	24	Ref. (1.00)	Ref. (1.00)
		≥55	610 (33.4)	33	2.16 (1.29-3.62)**	1.30 (0.76-2.24)	536 (31.2)	18	1.41 (0.76-2.59)	1.13 (0.61-2.09)
		Missing	281 (15.4)	19	2.17 (1.20-3.95)*	1.68 (0.92-3.09)	268 (15.6)	16	2.03 (1.07-3.84)*	1.78 (0.93-3.38)

[†]Multivariate adjustment for: 1) age group, 2) gender, 3) Charlson comorbidity index, 4) cirrhosis.
*Denotes p value $\leqslant 0.05$. **Denotes p value <0.01. ***Denotes p value <0.001.

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Further, 6.9%, 17.6% and 14.3% had a history of previous hospitalisation due to alcohol intoxication, violence-related injury and drug intoxication, respectively. A description of the overlap between health risk behaviour variables is provided in Supplementary Table 3.

Mortality events occurring after SVR

The total duration of follow-up in our cohort was 10,915 person-years. The mean and median duration of follow-up time per patient was 5.2 years and 5.9 years, respectively. In all, 78 deaths were observed. Nine deaths were due to primary liver cancer (eight deaths of which were cases of hepatocellular carcinoma, and one was a case of intrahepatic bile duct cancer); seven deaths were due to other liver-related causes; 18 deaths were drug-related; 5 deaths were due to external causes; 16 deaths were from non-liver cancers; 9 deaths were due to diseases of the circulatory system; and the remaining 14 deaths were from other causes. To note, lung cancer was the most common type of non-liver cancer death (N = 7), whilst chronic obstructive pulmonary disease was the most common type of "other" death (N = 4). Finally, the nine deaths from primary liver cancer occurred after a mean of 4.8 years of follow-up at ages ranging from 46–77 years.

Survival in SVR patients relative to the general population

Ten-year survival function

For all SVR patients, ten-year survival was 93.2% (95% CI: 91.2–84.8%) *vs.* 96.1% for the general population. For SVR patients without baseline cirrhosis, ten-year survival was 94.6% (95% confidence interval (CI): 92.7–96.1), *vs.* 96.3% for the general population (Fig. 1).

All-cause and cause-specific standardised mortality ratios

The number of all-cause deaths that would have been expected in our SVR cohort given general population mortality rates was 42. Thus with 78 deaths actually observed, the overall SMR was 1.86 (95% CI: 1.49–2.32). When confining the analysis to patients that had not been diagnosed with liver cirrhosis at baseline, the SMR fell to 1.55 (95% CI: 1.20–2.01). In terms of cause-specific SMRs (Table 2), significant elevations were observed for death due to primary liver cancer and death due to drug-related causes. The SMR for liver cancer was less pronounced in the subgroup of patients without diagnosed cirrhosis at baseline (SMR: 9.02; 95% CI: 2.91–27.96), than in the entire SVR cohort as a whole (SMR: 23.50; 95% CI: 12.23–45.16). In contrast, the SMR for drug-related mortality was comparable between all SVR patients (SMR: 6.58, 95% CI: 4.15–10.45), and SVR patients without baseline cirrhosis (SMR: 6.90, 95% CI: 4.35–10.96). We did not see any statistically significant differences in the SMRs for liver cancer mortality, all-cause mortality and drug mortality according to age (Fig. 3A). Finally, no statistically significant elevations were noted for the remaining cause-specific categories, including: other liver disease; external causes, diseases of the circulatory system; and non-liver cancers.

The absolute contribution of each cause to the overall excess

Drug-related mortality made the biggest absolute contribution to overall excess mortality (42% in all SVR patients, and 75% in SVR patients without baseline cirrhosis). Primary liver cancer accounted for 24% of the total excess in all SVR patients and 13% of the excess in SVR patients without cirrhosis. Taken together, these two causes of death accounted for 66% of all excess deaths in the SVR cohort as a whole, and 88% of all excess death in SVR patients without cirrhosis (Fig. 2). We further examined the absolute contribution of primary liver cancer and drug-related mortality in all SVR patients according to age during follow-up (Fig. 3B). In the under 50s, drug-related causes accounted for the majority of the excess death (53%), whilst the contribution of primary liver cancer was minimal (<5%). Conversely, in the over 50s, most of the excess (54%) was due to liver cancer, whilst drug-related mortality played a more minor role (accounting for only 26% of the excess).

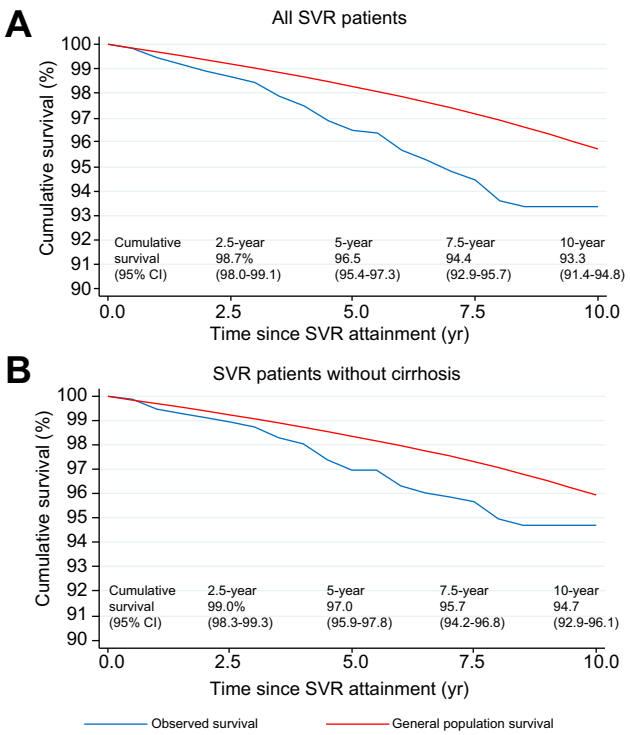

Fig. 1. Ten-year survival relative to the general population. For: (A) all SVR patients; and (B) SVR patients without cirrhosis. (This figure appears in colour on the web.)

Baseline factors associated with all-cause mortality

Ten factors were significantly associated (p <0.05) with an increased risk of post-SVR mortality following adjustment for age group and gender, cirrhosis and CCI (Table 1). These were as follows: older age; male gender; diagnosis of liver cirrhosis; high Charlson comorbidity score; past alcohol consumption ⩾50 units/week sustained for six months or more; history of intravenous drug use; past hospitalisation for alcohol intoxication; past hospitalisation for drug intoxication; and past hospitalisation for violence-related injury, and APRI <0.7.

Post-hoc analyses: generating a composite score for health risk behaviours

The five modifiable factors associated with post-SVR mortality were as follows: 1) past alcohol consumption ⩾50 units/week

Table 2. Cause-specific standardised mortality ratios (SMR) relative to the general population of Scotland. (i) For all SVR patients. (ii) SVR patients without cirrhosis at baseline.

No.	Cause of death	(I) All SVR patients (N = 1824)			(II) SVR patients without cirrhosis (N = 1717)		
		No. expected deaths	No. observed deaths	SMR (95% CI)	No. expected deaths	No. observed deaths	SMR (95% CI)
1	Primary liver cancer	0.4	9	23.50 (12.23-45.16)	0.3	3	9.02 (2.91-27.96)
2	Other liver-related (excluding liver cancer)	3.1	7	2.25 (1.07-4.71)	2.8	3	1.06 (0.34-3.30)
3	Drug-related	2.7	18	6.58 (4.15-10.45)	2.6	18	6.90 (4.35-10.96)
4	External causes	4.0	5	1.27 (0.53-3.04)	3.7	4	1.09 (0.41-2.89)
5	Non-liver cancer	12.6	16	1.27 (0.78-2.08)	11.0	14	1.28 (0.76-2.15)
6	Disease of the circulatory system	10.2	9	0.89 (0.46-1.70)	8.9	8	0.90 (0.45-1.79)
7	Other (i.e., none of the above)	9.1	14	1.54 (0.91-2.61)	8.1	8	0.99 (0.50-1.99)
1-2	All liver-related	3.5	16	4.57 (2.80-7.46)	3.2	6	1.90 (0.86-4.24)
3-7	All non-liver related	38.5	62	1.61 (1.26-2.07)	34.2	52	1.52 (1.16-2.00)
1-7	All-causes	42.0	78	1.86 (1.49-2.32)	37.4	58	1.55 (1.20-2.01)

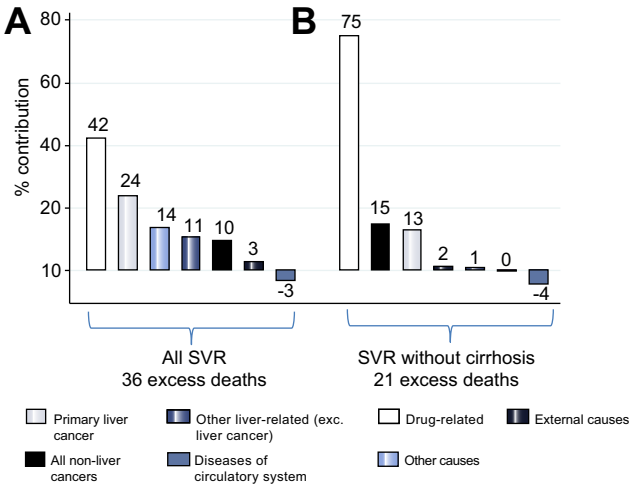

Fig. 2. Absolute contribution (%) to the overall excess for each cause of death. For (A) all SVR patients, and (B) SVR patients without cirrhosis at baseline.

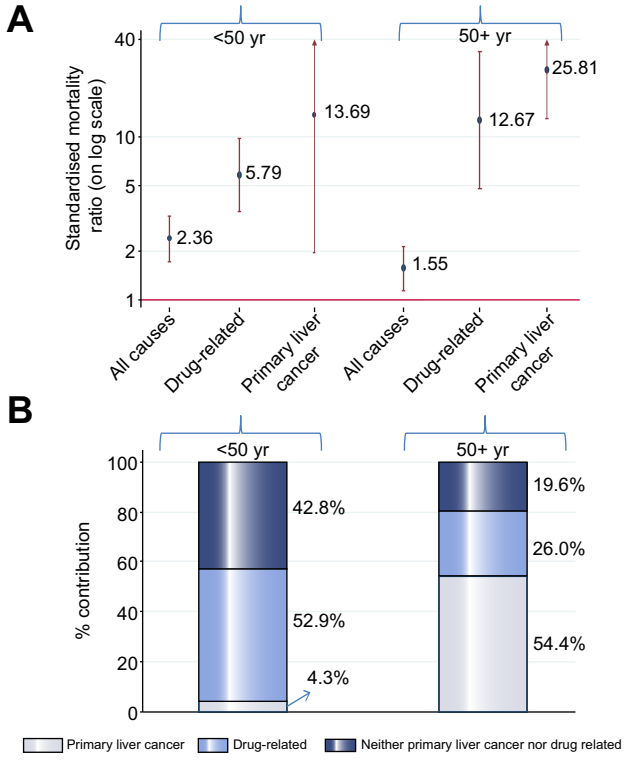

Fig. 3. For all SVR patients: (A) cause-specific standardised mortality ratios according to age, and (B) absolute contribution (%) to the overall excess for each cause of death, according to age. (This figure appears in colour on the web.)

sustained for six months or more; 2) history of intravenous drug use; 3) past hospitalisation for alcohol intoxication; 4) past hospitalisation for drug intoxication; and 5) past hospitalisation for violence-related injury heavy alcohol use. In a *post-hoc* analysis, we generated a 4-point composite score based on the presence or absence of these five factors (Fig. 4). The intention was to create a proxy marker for health risk behaviours present during follow-up. We calculated SMRs for all-cause mortality according to this composite score and observed a strong dose–response relationship (p value for trend, <0.001). Among all SVR patients with a score of zero (i.e., indicating the minimum level of health risk behaviour), the SMR was 0.70 (95% CI: 0.41–1.18), whereas for individuals with a score of 3 (i.e., the maximum score, indicating the highest level of health risk behaviour), the SMR was 6.19 (95% CI: 3.60–10.67). We also constructed a multivariate Cox regression model to assess the association between our behaviour score and the mortality hazard after adjusting for age, sex, cirrhosis, CCI and APRI (Table 3). We observed a stepwise change in the mortality hazard according to behaviour score. Among all SVR patients, the hazard was 2.12 times ($p = 0.035$), 4.25 times (p <0.001), and 7.28 times (p <0.001) higher for individuals with a score of 1, 2 and 3, respectively, relative to individuals with a score of zero.

Discussion

Main findings

The arrival of highly effective and tolerable antiviral regimens for chronic hepatitis C infection has set the stage for a rapid increase

Research Article

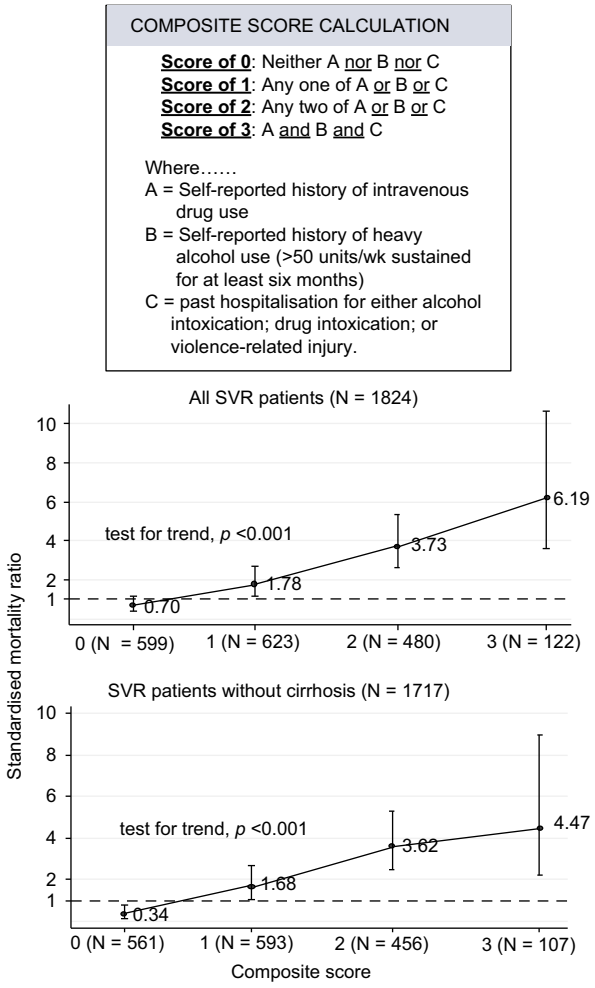

Fig. 4. Standardised mortality ratio according to baseline health risk behaviours. For all SVR patients, and SVR patients without cirrhosis.

in the number of persons living with SVR. Yet, our present understanding of the prognosis that this "cured" population face is incomplete. Although we know that SVR patients exhibit superior mortality and morbidity rates relative to non-SVR patients [3,13,18], we know little about how these rates compare to the broader general population. In the present study, we followed 1824 SVR patients up for 5.2 years on average, and observed mortality rates in excess of the general population. Specifically, among all SVR patients, mortality rates were almost 2-fold higher (SMR: 1.86; 95% CI: 1.49–2.32), whilst among SVR patients without a diagnosis of cirrhosis at baseline – a group who on the whole will tend to be discharged from specialist care without further follow-up – mortality rates were 1.6-fold higher (SMR: 1.55; 95% CI:1.20–2.01). Our cause-specific analyses (Table 2; Figs. 2 and 3) demonstrated two important points. Firstly, that the overall excess was driven, in the main, by a higher than expected frequency of death from liver cancer and death from drug-related causes. Secondly, that the contribution of these two causes differed with respect to age. Drug-related mortality accounted for 53% of all excess death in the under 50s (in comparison, only 4.3% of the excess death was due to primary liver cancer). Conversely, death from liver cancer accounted for 54% of all excess death in the over 50s (whereas, in this age group, only 26% of the excess death was due to drug-related causes).

The occurrence of primary liver cancer

The largest cause-specific SMRs were seen with respect to primary liver cancer. In our SVR cohort as a whole, the risk of dying from liver cancer was more than 20 times greater than the general population (SMR: 23.50; 95% CI: 12.23–45.16). Notably, an excess risk of dying from liver cancer remained – SMR: 9.02; 95% CI: 2.91–27.96 – after excluding individuals with diagnosed liver cirrhosis at baseline. This result requires careful interpretation. On the one hand, it could lend support to previous observations that the risk of liver cancer after SVR is not confined to cirrhotic patients, but extends more widely to some patients at the pre-cirrhosis stage [24–28]. Alternatively, it may reflect a high level of undiagnosed liver cirrhosis in our cohort (indeed, the potential for this is appreciable, given that the majority of patients had no record of a liver biopsy or FibroScan being conducted in the two years prior to baseline; Supplementary Table 4). To inform which interpretation is more valid, we reviewed the medical notes of the three "non-cirrhotic" individuals who went on to develop primary liver cancer (involving two deaths from hepatocellular carcinoma and one from intrahepatic bile duct carcinoma). Whilst two patients had indications of significant/-severe fibrosis, none of the three would have met the definition of compensated cirrhosis currently adopted by NHS England (Supplementary materials and methods), despite all having the requisite tests to do so on at least one level (i.e., all three had an APRI score and AST:ALT ratio pre-treatment; whilst one case had an ultrasound and another had a biopsy upon completion of therapy). Further, only one case was retained in on-going clinical follow-up post-SVR, whilst the other two were discharged. More research is arguably needed to inform which SVR patients can be safely discharged, versus which patients would benefit from regular HCC screening. However, we must stress that although the relative risk of a liver cancer death was high in the non-cirrhotic group (i.e., nine times higher relative to the general population), the absolute risk – both of liver cancer and indeed of any liver-related event - was still very low (<1% after 7.5 years; Supplementary Fig. 1).

Patient characteristics associated with post-SVR mortality

To understand how the elevated mortality rate in "cured" hepatitis C patients might be reversed, we carried out a regression analysis to identify modifiable predictors of all-cause mortality (Table 1). Ten predictive characteristics were identified in total, of which half – older age, male gender, liver cirrhosis; high CCI; and APRI <0.7 – were non-modifiable. But the remaining characteristics identified were markers of health risk behaviours (history of injecting drug use, history of heavy alcohol use, and past hospitalisation for violence, drug intoxication or alcohol intoxication) that, in principle at least, can be reversed. We created a composite score to approximate the degree of health risk behaviours present during follow-up (Fig. 4). The strong correlation between this composite score and the all-cause SMR suggests two things. Firstly, that health risk behaviours exert a strong influence on the extent to which mortality exceeds general population levels. Secondly, where health risk behaviours are minimal (i.e., as indicated by a score of zero) all-cause mortality

Table 3. Multivariate model including health risk behaviours composite score, for (i) all SVR patients (N = 1824); (ii) SVR patients without cirrhosis (N = 1717).

Category	Variable	(I) All SVR patients (N = 1824)		(II) SVR patients without cirrhosis (N = 1717)	
		Adjusted hazard ratio (95% CI)	*p* value	Adjusted hazard ratio (95% CI)	*p* value
Composite health risk behaviour score	0 (most favourable)	Ref. (1.00)	\	Ref. (1.00)	\
	1	2.12 (1.05-4.25)	0.035	3.74 (1.47-9.57)	0.006
	2	4.25 (2.15-8.41)	<0.001	7.22 (2.89-18.05)	<0.001
	3 (least favourable)	7.28 (3.29-16.08)	<0.001	10.42 (3.54-30.68)	<0.001
Basic demographics	(i) Age group				
	<35 yr	Ref. (1.00)	\	Ref. (1.00)	\
	35-49 yr	1.60 (0.81-3.18)	0.177	1.58 (0.46-1.49)	0.197
	50 +yr	3.80 (1.80-8.01)	<0.001	3.32 (1.48-7.46)	0.004
	(ii) Gender				
	Female	Ref. (1.00)	\	Ref. (1.00)	\
	Male	2.11 (1.12-3.94)	0.020	1.82 (0.91-3.64)	0.089
Medical co-morbidities	(iii) Diagnosed with cirrhosis				
	No	Ref. (1.00)	\	\	\
	Yes	3.31 (1.81-6.02)	<0.001	\	\
	(iv) Charlson co-morbidity index				
	None (0)	Ref. (1.00)	\	Ref. (1.00)	\
	Medium (1-2)	0.88 (0.52-1.46)	0.614	0.89 (0.51-1.55)	0.67
	High (3+)	3.01 (1.44-6.26)	0.003	3.45 (1.31-9.09)	0.012
Liver function tests	(xi) Mean AST-to-platelet ratio-index				
	<0.7 (mild fibrosis)	Ref. (1.00)	\	Ref. (1.00)	\
	≥0.7 (non-mild fibrosis)	0.49 (0.26-0.92)	0.025	0.50 (0.25-1.02)	0.058
	Missing	0.73 (0.42-1.27)	0.269	0.83 (0.46-1.49)	0.525

rates are equivalent to and even lower than the general population.

From the non-modifiable predictors identified in this study, the increased mortality risk associated with APRI <0.7 (*vs.* APRI ⩾0.7) was unexpected and at first glance paradoxical (Table 1). Subsequent interrogation revealed however that this association was very cause-specific, being driven only by an increased risk for drug mortality (Supplementary Fig. 2). The association overall therefore is probably due to residual confounding. Mild disease will be associated with more recent acquisition of HCV (given that fibrosis increases with duration of infection), which in turn will be associated with active drug use. With more robust data on active drug use at baseline, we would therefore not expect an association with APRI <0.7 to persist.

Consistency with previous work

Our finding of higher mortality in SVR patients relative to the general population is not supported by two previous studies. In a cohort of 192 SVR patients with F3-F4 fibrosis and an average age of 49 years, Van der Meer *et al.* observed a 10-year survival rate of 91.1% [17]. This was on par with survival in the general population. More recently, Bruno *et al.* reported 10-year survival of 90.9% for 177 SVR cirrhotic patients with a mean age of 59 years [18]. Again, this 10-year survival was comparable to the general population. In contrast, for the present study, we followed up a much larger (N = 1824), younger (mean age of 40.7 years) and more inclusive (comprising patients across the fibrosis continuum – not just those at an advanced end) group of SVR patients. Conversely, the 10-year survival that we observed of 93.2% was significantly lower than the 96.2% survival expected for the general population taking age, sex and calendar period into account. In overall terms, 86% more deaths were observed during our study than would have been expected under general population mortality rates (i.e., 78 deaths observed *vs.* 42 expected). One possible explanation for the higher mortality rate in our study could be selection bias. The patients in our Scottish cohort represent the vast majority (>80%) of individuals attaining SVR in Scotland over the 1996–2011 time-frame of this study. In contrast, the two previous studies were largely made up of individuals with biopsy-proven advanced liver fibrosis that attended a small number of tertiary clinics that may not accurately reflect the wider SVR population. Clearly more studies, from a variety of cohorts, are required to form a complete picture on this issue. Otherwise, our results concur with a prior analysis from Scotland reporting increased hospitalisation rates in SVR patients relative to the general population [29]. Our results are also consistent with a nationwide cohort study from Denmark [30]. In this study, Omland *et al.* observed that individuals who clear HCV infection spontaneously (not via treatment albeit) had higher overall mortality than the general population. However, – in line with this study (Fig. 4) – mortality was more comparable to the general population in subgroups without a history of alcohol and drug abuse.

Limitations of this study

There are several limitations in this analysis to highlight. Cirrhosis was diagnosed in only 5.8% of patients at baseline, however

due to inadequate testing, this is likely to be an underestimate of the true fraction with cirrhosis. Indeed, Supplementary Table 4 shows that only 44% of patients received a liver biopsy or a FibroScan in the two years prior to SVR attainment, which highlights the lack of uniform cirrhosis surveillance in our cohort. Potentially, undiagnosed liver cirrhosis could explain why we observed six liver deaths in our non-cirrhotic group, albeit we think that this is unlikely because when we reviewed the medical notes of the 3 "non-cirrhotic" patients who developed liver cancer, we did not find anything to suggest that these individuals were cirrhotic in reality. Another limitation is that we had no information on the socioeconomic status of patients in this cohort. Because HCV infection disproportionately affects people of lower socioeconomic status, and lower socioeconomic status is in turn associated with higher mortality rates [31], the omission of this variable could have inflated our survival differences. Thirdly, our data on health risk behaviours are limited in that they relate only to the baseline time-point, and mostly focus on only the extremes of alcohol and drug use. Future studies correcting for these weaknesses and additionally examining the impact of other major health behaviours – tobacco smoking, physical activity and diet – would be valuable. Fourthly, patients in our cohort were treated with either standard IFN ± ribavirin, or pegylated IFN ± ribavirin. These regimens are long (16–48 weeks) and entail significant adverse effects. As a result, patients would typically have received intensive coaching from clinicians and nursing staff (and this coaching would have applied especially to SVR patients who, given futility stopping rules, remain in the treatment window for longer than non-SVR patients). We have previously speculated that this coaching and/or the euphoria of attaining SVR may have an important galvanising effect on patients with regard to encouraging more salubrious health behaviours [19]. Thus, in the impending era of highly tolerable, accessible and efficacious antiviral therapy – i.e., an era that will obviate the same level of patient coaching and patient commitment – a very different post-SVR picture could emerge. It will be important to repeat this analysis five years hence. Finally, we did not have robust data on diabetes mellitus status and obesity despite these conditions being recognised determinants of liver sequelae in the SVR population [32].

Summary

In this large nationwide Scottish cohort, mortality in patients with a hepatitis C "cure" was higher than the general population. The excess was mainly driven by death from liver cancer and death from drug-related causes. Health risk behaviours emerged as the major modifiable risk factor for mortality in this population underlining the importance of a multidisciplinary approach to HCV that addresses lifestyle risk factors in addition to viral infection. On this note the SVR time-point may be a particularly opportune moment to assess what other services and support the patient may be in need of. To minimise the post-SVR risk of HCC, careful and prudent staging of liver fibrosis should be performed prior to discharge to identify those patients who might benefit from regular screening. Arguably, more research is needed to bottom out more precisely which SVR patients stand to benefit from such surveillance. As a final aside, this analysis has bearing on the new World Health Organization (WHO) targets to cut global death from hepatitis B and C by 10% before 2020, and by 65% by 2030 [33].

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Conflicts of interest

HI reports personal fees from Gilead, outside the submitted work. PH has received personal support from Roche, Janssen, MSD and Gilead. JD reports grants and personal fees from Roche, grants and personal fees from MSD, grants and personal fees from Janssen, grants and personal fees from Gilead, personal fees from BMS, grants from GSK, grants and personal fees from Abbvie, outside the submitted work. DG reports personal fees from Abbvie, personal fees from Gilead and MSD, outside the submitted work. SB reports personal fees from Abbvie, personal fees from BMS, personal fees from Gilead, personal fees from Janssen, personal fees from MSD, outside the submitted work; RF reports receiving advisory board/speaker's fees from Janssen, Gilead, BMS, Merck and Abbvie. NK reports participation in Advisory Boards for Gilead, Merck, Abbvie, and Janssen, outside the submitted work. SH reports grants from Health Protection Scotland, during the conduct of the study; personal fees from Abbvie, personal fees from Gilead, outside the submitted work. All other authors have nothing to disclose.

Authors' contributions

HI carried out the statistical analyses and drafted the manuscript. All authors were involved in the study design; collection of data; interpretation of data; and the editing of the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2016.08.004.

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