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MAJOR ARTICLE

# All-Cause Mortality and Causes of Death in the Swiss Hepatitis C Cohort Study (SCCS)

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***Background.*** With direct-acting antiviral agents (DAAs), mortality rates and causes of death among persons with hepatitis C virus (HCV) infection may change over time. However, the emergence of such trends may be delayed by the slow progression of chronic hepatitis C. To date, detailed analyses of cause-specific mortality among HCV-infected persons over time remain limited.

***Methods.*** We evaluated changes in causes of death among Swiss Hepatitis C Cohort Study (SCCS) participants from 2008 to 2016. We analyzed risk factors for all-cause and cause-specific mortality, accounting for changes in treatment, fibrosis stage, and use of injectable drugs over time. Mortality ascertainment was completed by linking lost-to-follow-up participants to the Swiss Federal Statistical Office death registry.

***Results.*** We included 4700 SCCS participants, of whom 478 died between 2008 and 2016. The proportion of unknown causes of death decreased substantially after linkage, from 42% to 10%. Leading causes of death were liver failure (crude death rate 4.4/1000 person-years), liver cancer (3.4/1000 person-years), and nonliver cancer (2.8/1000 person-years), with an increasing proportion of cancer-related deaths over time. Cause-specific analysis showed that persons with sustained virologic response were less at risk for liver-related mortality than those never treated or treated unsuccessfully.

***Conclusions.*** Although the expected decrease in mortality is not yet observable, causes of death among HCV-infected persons have evolved over time. With the wider use of DAAs, liver-related mortality is expected to decline in the future. Continued monitoring of cause-specific mortality will remain important to assess the long-term effect of DAAs and design effective interventions.

**Keywords.** cohort; hepatitis C; mortality; risk factors; Switzerland.

Hepatitis C virus (HCV) infection is a leading cause of liver-related mortality [1, 2], responsible for about 399 000 deaths worldwide in 2016. With the introduction of potent direct-acting antiviral agents (DAAs), the risk of morbidity and mortality for HCV-infected persons has decreased substantially [3]. Causes of death are likely changing over time and with age, as HCV-infected people may become increasingly at risk of dying from non-liver-related causes, including non-liver-related malignancies or cardiovascular diseases [4]. However, due to the slow natural progression of chronic hepatitis C and the increasing number of treatments available, such trends may be slow to emerge. Some studies predict a rise in liver-related deaths to continue for another decade [5, 6]; meanwhile, the number of HCV-related deaths is stable or increasing in many settings [7].

Various studies have analyzed mortality among HCV-infected persons. In the United States, several studies have shown that HCV-related deaths disproportionally affect persons born between 1945 and 1965 [8, 9]. Both a comparison between the Chronic Hepatitis Cohort Study and the official death certificates in the United States [9] and a comparison between the Swiss Hepatitis C Cohort Study (SCCS) and the death certificates from the Swiss Federal Statistical Office (SFSO) [7] showed that under-reporting of HCV infection on death certificates is quite common. In both the United States and Switzerland, HCV-related mortality increased significantly between the late 1990s and the early 2000s, whereas HIV-related mortality decreased and hepatitis B virus (HBV)–related mortality remained relatively stable [7, 8]. In New South Wales, Australia, HCV notifications were linked to the death registry [1, 2]. When comparing mortality between HCV-infected

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persons and the general population, both liver-related and drug-related death rates were about 15–16 times higher in Australians with HCV. In HCV-mono-infected persons, liver-related deaths increased considerably with older age, and drug-related death rates were higher in younger age groups [1, 2]. In this population, liver-related mortality remained stable between 1997 and 2006, and drug-related mortality was relatively constant between 2002 and 2006 [1, 2]. More recently, a study based on the US Veterans Affairs Hepatitis C Clinical Case Registry showed that, among HCV-infected patients treated with DAAs, successful treatment substantially reduced mortality, both in the presence and absence of advanced liver disease [10, 11].

Nevertheless, few studies have analyzed detailed patterns of cause-specific mortality among HCV-infected persons [12, 13]. We therefore investigated the risk factors and time trends for all-cause and cause-specific mortality among HCV-infected persons in the SCCS. We improved mortality ascertainment by linking patients who were lost to follow-up to death certificates from the SFSO.

## METHODS

The SCCS is a prospective observational cohort study, established in 2000, that continuously enrolls patients aged ≥18 years in Switzerland. Only persons who are confirmed to be anti-HCV antibody–positive are included [14]. Eight centers are involved, including all 5 university hospitals in Switzerland (Basel, Bern, Geneva, Lausanne, Zürich), 3 large nonuniversity hospitals (Lugano, Neuchâtel, and St. Gallen), and some affiliated centers. For all persons in the SCCS, various demographic, psychosocial, clinical, laboratory, and treatment data were collected via standardized questionnaires. The questionnaires were completed by physicians or study nurses during enrollment and at annual follow-up visits. The study was approved by all local ethics committees, and all persons provided written informed consent. For deceased persons, the cause of death was coded according to the International Statistical Classification of Diseases (ICD-10) [15]. Supplementary information was also provided to specify if the death was related to HCV infection or due to an accident, a suicide, or overdose/accidental poisoning.

We included all persons enrolled before December 31, 2016 (until when data on causes of death were compiled by the SFSO). We excluded those who died before January 1, 2008, because the new 13-digit social security number (SSN), which was needed for the linkage, became available only in 2008. Patients were lost to follow-up (LTFU) if they were not seen since August 2015 and not known to have moved abroad or to have died. Sustained virologic response (SVR) was defined as an undetectable HCV RNA ≥12 weeks after the end of antiviral treatment.

The SFSO has monitored causes of death in Switzerland since 1876. Causes of death are coded by ICD-10 codes based on initial, consecutive, and concomitant diseases listed on the SFSO death certificate [16]. To complete the SCCS information on mortality, all SCCS participants who were declared LTFU or dead between January 1, 2008, and December 31, 2016, were linked to the SFSO death registry by exact record linkage. When the 13-digit SSN was available, we used it as well as the date of birth as linkage keys. If the SSN was not available, linkage was based on the dates of birth and death.

We classified the main cause of death into mutually exclusive categories as described in Table 1. The "other" category includes all causes with a frequency <30 persons. Unnatural causes of death include suicide, overdose/accidental poisoning, and accident.

For each deceased person, we retained 1 source of information to classify the cause according to the following rules. For persons linked to the death registry, we preferentially selected ICD-10 codes from the SFSO. When this information was not available or when the SFSO provided less specific information than the SCCS, we used the ICD-10 code from the SCCS. In case no ICD-10 code was available from the SFSO or the SCCS, we used the supplementary information from the SCCS on causes of death mentioned earlier. All the deceased persons who could not be classified following this procedure were defined as "unspecified." Finally, the cause of death classification was reviewed by an expert clinician who corrected misclassifications of complex cases specific to HCV infection.

**Table 1. Categories of Causes of Death**

| Death Cause Group | Eligibility Criteria |
|---|---|
| Liver failure (other than liver cancer) | Selected ICD-10 codes:<br>B15–B19 (viral hepatitis)<br>B94.2 (sequelae of viral hepatitis)<br>K70 (alcoholic liver disease)<br>K71–K77 (toxic/chronic/other liver disease)<br>T86.4 (liver transplant failure and rejection)<br>Z94.4 (liver transplant status)<br>OR<br>Death identified as physically related to HCV infection according to information obtained at or after a SCCS visit |
| Liver cancer | Selected ICD-10 code: C22 |
| Nonliver cancer | Selected ICD-10 codes:<br>C00–C21, C23–C97 (all malignant neoplasms except liver cancer, including leukemia)<br>D00–D48 (all in situ, benign, and unknown neoplasms) |
| Unnatural cause | Selected ICD-10 codes:<br>S00–T88 except T86.4 (injury, poisoning, and certain other consequences of external cause)<br>V01–Y98 (external causes of morbidity and mortality)<br>Z92–Z99 except Z94.4 (health service–related factor)<br>OR<br>Death identified as due to accident, suicide, or overdose of narcotics according to the SCCS |
| Cardiovascular | Selected ICD-10 codes:<br>I00–I99 (diseases of the circulatory system) |
| Other | All the deaths with selected ICD-10 code not entering any of the criteria described above |
| Unspecified | No selected ICD-10 code and no complementary information from the SCCS |

Abbreviations: HCV, hepatitis C virus; ICD-10, *International Classification of Diseases, 10th revision*; SCCS, Swiss Hepatitis C Cohort Study.

For deceased persons linked to the SFSO death registry, we compared the main causes of death in the SCCS and the SFSO. We measured the interrater agreement via Kappa statistics [17] first by directly comparing the ICD-10 codes for the main cause of death and then by using the grouped causes of death (Table 1).

We calculated crude mortality rates overall and for different time periods, both for all-cause mortality and individual death cause groups. We also conducted survival analysis, for which follow-up time was calculated from enrollment into the cohort or starting date of the period of interest (baseline) to the censoring date (which was either the date of death or the last known date of being alive). When the dates of death in the SCCS and SFSO were different, we used the date from the SFSO.

We calculated crude cumulative incidences for each cause of death group, accounting for competing risk (each cause of death being a competing risk for the other causes) using the R *mstate* package [18]. We used univariable and multivariable Cox proportional hazard regression, including time-dependent covariables [18, 19], to determine risk factors of mortality. We first analyzed all-cause mortality, and then cause-specific mortality, for each of the causes of death (except for "other" and "unspecified"). Analyses were adjusted for sex, baseline age (as a continuous variable with restricted cubic splines [20]), fibrosis score (F1 to F4), history of injection drug use (IDU; ever, never), and treatment status (never treated, treated with SVR, treated without SVR). For all-cause mortality, we also accounted for the treatment history (never treated, ever treated and received DAA, ever treated but never received DAA). Due to the limited number of deceased patients who received DAAs, we could not add this covariable in the cause-specific analysis. To determine the fibrosis score, we combined information from liver biopsies, FibroScan analyses, and any reported cirrhosis during follow-up. Liver stiffness assessed by FibroScan was converted to Metavir scores (F1: <7.5 kPa; F2: ≥7.5 to <9.5 kPa; F3: ≥9.5 to <12.5 kPa; F4: ≥12.5 kPa), and reported cirrhosis was translated into Metavir score F4. We made no assumption on the possible evolution of fibrosis over time and carried the values forward until the next measurement or until the end of the study. We used multiple imputation by chained equations (R *mice* package [21]) to impute missing values of time-dependent covariables for the multivariable analysis (see details in the Supplementary Data).

For sensitivity analysis, we recalculated multivariable Cox proportional hazard models without multiple imputation, excluding all persons with incomplete information on treatment type and outcome, fibrosis score, and history of IDU at any time over the period of interest.

## RESULTS

A total of 4700 SCCS participants were followed between January 1, 2008, and December 31, 2016, with 471 of them (10%) reported to be deceased. The SSN was available for 66.0% (311 of 471) of persons, and for 30.4% (143 of 471) of persons the SSN was missing but the date of death was known. In addition, 245 of the followed persons were LTFU, and 214 (87.3%) had an SSN. Overall, 361 of the 471 deceased patients and 7 of the LTFU patients were linked to the SFSO death registry. Figure 1 summarizes the flowchart of the SCCS-SFSO linkage. Among the linked persons, the reported date of death was identical for 298 persons, was different for 54 persons (for 11, the difference was ±1 day), and was missing for 16 persons (including the 7 persons LTFU who were linked).

After linkage, the date of death was known for 474 of the 478 deceased persons and remained unknown for 4 persons. The median individual duration of follow-up (interquartile range [IQR]) was 6.5 (2.2–9.0) years. During a total of 26 114 person-years (pyrs) of follow-up, the overall mortality rate was 18.3/1000 pyrs (95% CI, 16.7–20.0).

Table 2 shows the baseline characteristics of all the included SCCS persons and of deceased persons who could or could not be linked to the death registry. Persons were mostly male (61.7%),

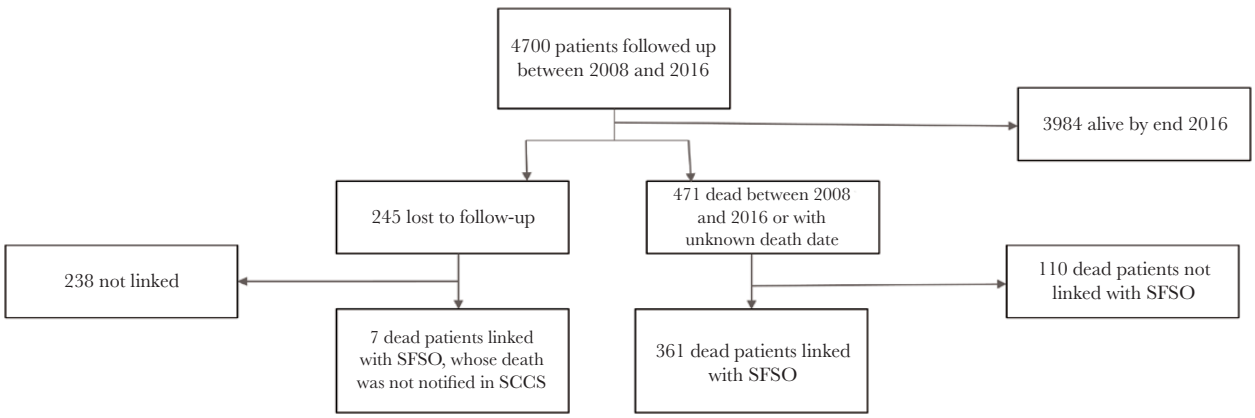


**Figure 1.** Flowchart illustrating the linkage between the Swiss Hepatitis C Cohort Study (SCCS) and the death registry of the Swiss Federal Office of Statistics (SFSO).

**Table 2. Characteristics of Study Participants at Baseline and Causes of Death in the Swiss Hepatitis C Cohort Study; *P* Values From Kruskal-Wallis Rank-Sum Test for Continuous Variables and Chi-Square Test for Categorical Variables Are Shown**

| | | All (n = 4700) | Death (n = 478) | Death Linked (n = 368) | Death Not Linked (n = 110) | *P* Value Linked, VS Not Linked |
|---|---|---|---|---|---|---|
| Sex | Male | 2901 (61.72) | 338 (70.71) | 259 (70.38) | 79 (71.82) | .86 |
| | Female | 1799 (38.28) | 140 (29.29) | 109 (29.62) | 31 (28.18) | |
| Nationality | Swiss | 3456 (73.53) | 372 (77.82) | 291 (79.08) | 81 (73.64) | .28 |
| | Other | 1235 (26.28) | 106 (22.18) | 77 (20.92) | 29 (26.36) | |
| | Unknown | 9 (0.19) | X | X | X | |
| Age at baseline, y | | 47.5 (40.6–55.1) | 51.8 (44.5–60) | 52 (45–60.1) | 50.9 (43.3–57.2) | .31 |
| Age at death census, y | | 53.5 (46.4–60.5) | 56 (48.5–64.7) | 56.3 (50.4–65.3) | 53.6 (46.1–60) | .01 |
| Time from baseline to death census, y | | 6.5 (2.2–9) | 4 (2–6.5) | 4.9 (2.9–6.8) | 1.6 (0.6–3.5) | <.001 |
| Treatment at baseline | No | 2910 (61.91) | 263 (55.02) | 194 (52.72) | 69 (62.73) | NA |
| | DAA (IFN-free) | 33 (0.7) | X | X | X | |
| | IFN-based | 1757 (37.38) | 215 (44.98) | 174 (47.28) | 41 (37.27) | |
| IDU at baseline | Never | 1780 (37.87) | 182 (38.08) | 142 (38.59) | 40 (36.36) | .78 |
| | Ever | 2578 (54.85) | 263 (55.02) | 201 (54.62) | 62 (56.36) | |
| | Unknown | 342 (7.28) | 33 (6.9) | 25 (6.79) | 8 (7.27) | |
| Fibrosis score at baseline | F0, F1, or F2 | 2538 (54) | 160 (33.47) | 123 (33.42) | 37 (33.64) | .42 |
| | F3 or F4 | 1261 (26.83) | 229 (47.91) | 185 (50.27) | 44 (40) | |
| | Unknown | 901 (19.17) | 89 (18.62) | 60 (16.3) | 29 (26.36) | |
| Treatment status at baseline | Never treated | 2910 (61.91) | 263 (55.02) | 194 (52.72) | 69 (62.73) | .12 |
| | Treated with SVR | 693 (14.74) | 44 (9.21) | 35 (9.51) | 9 (8.18) | |
| | Treated with failure | 941 (20.02) | 144 (30.13) | 119 (32.34) | 25 (22.73) | |
| | Treated, outcome unknown | 156 (3.32) | 27 (5.65) | 20 (5.43) | 7 (6.36) | |
| BMI at baseline | | 24.1 (21.6–27.1) | 24.9 (21.6–28.5) | 24.8 (21.6–28.4) | 25.7 (21.8–30.8) | .26 |
| HIV coinfection at baseline | No | 3204 (68.17) | 326 (68.2) | 252 (68.48) | 74 (67.27) | .24 |
| | Yes | 258 (5.49) | 51 (10.67) | 35 (9.51) | 16 (14.55) | |
| | Unknown | 1238 (26.34) | 101 (21.13) | 81 (22.01) | 20 (18.18) | |
| Cirrhosis at baseline | No | 3259 (69.34) | 213 (44.56) | 165 (44.84) | 48 (43.64) | .84 |
| | Yes | 828 (17.62) | 207 (43.31) | 163 (44.29) | 44 (40) | |
| | Unknown | 613 (13.04) | 58 (12.13) | 40 (10.87) | 18 (16.36) | |
| Diabetes mellitus at baseline | No | 4019 (85.51) | 336 (70.29) | 274 (74.46) | 62 (56.36) | .01 |
| | Yes | 275 (5.85) | 52 (10.88) | 33 (8.97) | 19 (17.27) | |
| | Unknown | 406 (8.64) | 90 (18.83) | 61 (16.58) | 29 (26.36) | |
| Alcohol consumption at baseline | Light | 2952 (62.81) | 268 (56.07) | 199 (54.08) | 69 (62.73) | .11 |
| | Former | 348 (7.4) | 43 (9) | 38 (10.33) | 5 (4.55) | |
| | Heavy | 749 (15.94) | 111 (23.22) | 91 (24.73) | 20 (18.18) | |
| | Moderate | 563 (11.98) | 46 (9.62) | 34 (9.24) | 12 (10.91) | |
| | Unknown | 88 (1.87) | 10 (2.09) | 6 (1.63) | 4 (3.64) | |
| Cause of death | Cardiovascular | 33 (0.7) | 33 (6.9) | 26 (7.07) | 7 (6.36) | NA |
| | Liver cancer | 89 (1.89) | 89 (18.62) | 84 (22.83) | 5 (4.55) | |
| | Liver failure | 114 (2.43) | 114 (23.85) | 99 (26.9) | 15 (13.64) | |
| | Nonliver cancer | 72 (1.53) | 72 (15.06) | 65 (17.66) | 7 (6.36) | |
| | Other | 59 (1.26) | 59 (12.34) | 41 (11.14) | 18 (16.36) | |
| | Unnatural | 65 (1.38) | 65 (13.6) | 53 (14.4) | 12 (10.91) | |

Abbreviations: BMI, body mass index; DAA, direct-acting antiviral agent; IDU, injection drug use; IFN, interferon; SVR, sustained virologic response; VS, versus.

Swiss nationals (73.5%), and their median age at start of follow-up (IQR) was 47.5 (40.6–55.1) years. The majority (54.9%) had a history of IDU, 38.8% had received antiviral treatment, and 17.6% were cirrhotic. Deceased persons who could or could not be linked to the death registry had similar characteristics.

Of the 368 deaths linked to the death registry, the main cause of death was available from both SCCS and SFSO for 249 persons (67.7%), and for 227 of these (91.1%) ICD-10 codes were provided in the SCCS. When comparing causes of death using ICD-10 codes, the Kappa statistic was 0.14 (40 of 227 with identical codes). If using grouped causes of death, the Kappa statistics increased to 0.45 (138 of 249 with identical causes): The agreement was weak for both approaches. A comparison of death cause groups retrieved from the SCCS and from the SFSO for persons with information on cause of death from both sources is available in the Supplementary Data.

Liver failure was the leading cause of death, with a crude death rate of 4.4/1000 pyrs (95% CI, 3.6–5.2), followed by liver cancer (3.4/1000 pyrs; 95% CI, 2.8–4.2), nonliver cancer (2.8/1000 pyrs; 95% CI, 2.2–3.4), unnatural causes (2.5/1000 pyrs; 95% CI, 2.0–3.1), other causes (2.3/1000 pyrs; 95% CI, 1.8–2.9), and cardiovascular causes (1.3/1000 pyrs; 95% CI, 0.9–1.7). For 46 of the 478 deceased persons (10%), the main cause of death was unknown.

Figure 2 shows the evolution of crude mortality rates for all-cause, liver failure, and liver cancer mortality over time. Similar curves for all the cause-of-death groups listed in Table 1. Before 2014, the leading cause of death was liver failure, followed by liver cancer and nonliver cancer. In contrast, after 2014, when DAA became more widely available in Switzerland, liver cancer became the leading cause of death, followed by liver failure and nonliver cancer.

Figure 3 shows the cumulative incidence of causes of death over time. The overall probability of dying from any cause increased from 1.5% after 1 year of follow-up to 13.8% after 8 years. While liver failure remained the most common cause of death throughout the follow-up period, liver cancer increased in relative proportion from year 6 onwards.

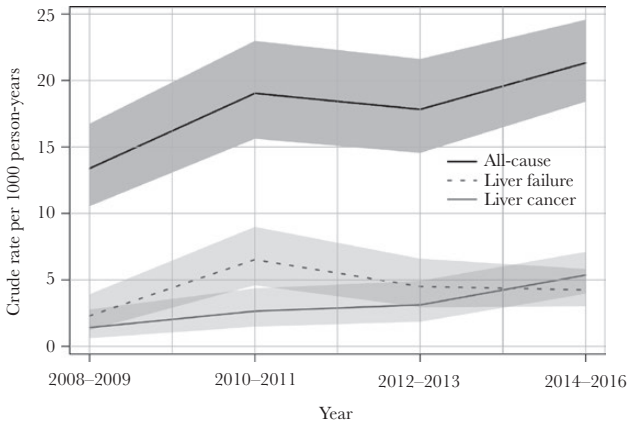


**Figure 2.** Crude mortality rates over the years for all-cause mortality, liver failure, and liver cancer mortality in the Swiss Hepatitis C Cohort Study.

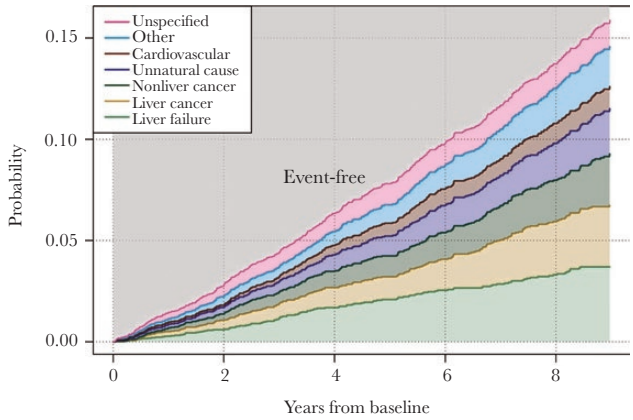


**Figure 3.** Cumulative incidence of different causes of death since registration in the Swiss Hepatitis C cohort study (causes of death are in the same order in the legend and on the plot).

Table 3 shows the risk factors from the multivariable Cox models for all-cause and cause-specific mortality in the SCCS over the period 2008–2016. Results from the univariable Cox models are presented in the Supplementary Data.

For all-cause mortality, the risk of death was increased for men, older persons, those with a high fibrosis stage (hazard ratio [HR], 3.62; 95% CI, 2.92–4.49; for those with a fibrosis score ≥F3 compared with ≤F2), and those with a history of IDU (HR, 2.01; 95% CI, 1.57–2.58). Compared with persons who were never treated, the risk of death was lower for

**Table 3. Estimates of the Effect of Gender, Age, Treatment, Fibrosis Stage, and IDU on Mortality, From Multivariable Cox Regression Models (A) for All-Cause Mortality and (B) for Cause-Specific Mortality**

**A, All-Cause Mortality**

| | Total: 4700 Persons | All-Cause (478 Deaths) |
|---|---|---|
| Sex | | *P* < .001 |
| | Male | 1.0 (ref) |
| | Female | 0.68 (0.56–0.84) |
| Age at baseline, y | | *P* < .001 |
| | 20 | 0.6 (0.37–0.97) |
| | 40 | 1.0 (ref) |
| | 60 | 2.51 (2.04–3.1) |
| Treatment status | | *P* < .001 |
| | Never treated | 1.0 (ref) |
| | Treated with DAA, SVR | 0.24 (0.09–0.63) |
| | Treated with DAA, failure | 0.86 (0.27–2.75) |
| | Treated with IFN, SVR | 0.34 (0.25–0.46) |
| | Treated with IFN, failure | 0.86 (0.69–1.06) |
| Fibrosis score | | *P* < .001 |
| | F0, F1, or F2 | 1.0 (ref) |
| | F3 or F4 | 3.62 (2.92–4.49) |
| IDU | | *P* < .001 |
| | Never | 1.0 (ref) |
| | Ever | 2.01 (1.57–2.58) |

**Table 3. Continued**

**B, Cause-Specific Mortality**

| | | Liver Failure | Liver Cancer | Nonliver Cancer | Cardiovascular | Unnatural Cause |
|---|---|---|---|---|---|---|
| | Total: 4700 Persons | (114 Deaths, 23.8%) | (89 Deaths, 18.6%) | (72 Deaths, 15.1%) | (33 Deaths, 6.9%) | (65 Deaths, 13.6%) |
| Sex | | | | | | |
| | Male | *P* = .17 | *P* = .097 | *P* = .073 | *P* = .043 | *P* = .18 |
| | Female | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) |
| | | 0.75 (0.49–1.14) | 0.67 (0.42–1.08) | 0.61 (0.36–1.05) | 0.44 (0.2–0.97) | 0.68 (0.39–1.19) |
| Age at baseline, y | | | | | | |
| | 20 | *P* = .019 | *P* < .001 | *P* < .001 | *P* < .001 | *P* = .045 |
| | 40 | 0.27 (0.08–0.93) | 0.09 (0.01–0.63) | 0.05 (0.01–0.28) | 0.64 (0.07–5.47) | 2.9 (1.21–6.9) |
| | 60 | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) |
| | | 2.06 (1.25–3.42) | 6.23 (2.72–14.24) | 8.34 (3.96–17.58) | 5.4 (2.13–13.72) | 1.06 (0.61–1.86) |
| Treatment status | | | | | | |
| | Never treated | *P* < .001 | *P* < .001 | *P* = .27 | *P* = .18 | *P* = .17 |
| | Treated with SVR | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) |
| | Treated with failure | 0.18 (0.08–0.37) | 0.33 (0.16–0.71) | 0.59 (0.31–1.11) | 0.42 (0.15–1.12) | 0.5 (0.24–1.03) |
| | | 0.78 (0.51–1.18) | 1.34 (0.81–2.22) | 0.84 (0.47–1.49) | 0.61 (0.26–1.41) | 0.89 (0.48–1.67) |
| Fibrosis score | | | | | | |
| | F0, F1, or F2 | *P* < .001 | *P* < .001 | *P* = .12 | *P* = .0095 | *P* = .028 |
| | F3 or F4 | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) |
| | | 13.8 (7.69–24.75) | 14.09 (6.59–30.13) | 1.52 (0.9–2.58) | 2.81 (1.29–6.14) | 1.91 (1.07–3.4) |
| IDU | | | | | | |
| | Never | *P* = .26 | *P* = .19 | *P* < .001 | *P* = .17 | *P* = .0011 |
| | Ever | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) |
| | | 1.31 (0.82–2.11) | 1.46 (0.83–2.56) | 3.22 (1.64–6.33) | 2.12 (0.73–6.18) | 3.65 (1.67–7.97) |

Abbreviations: DAA, direct-acting antiviral agent; IDU, injection drug use; IFN, interferon; SVR, sustained virologic response.

treated persons who reached SVR after receiving interferon (IFN)-based treatment (HR, 0.33; 95% CI, 0.24–0.45), and even slightly lower for treated persons who reached SVR after receiving DAAs (HR, 0.23; 95% CI, 0.08–0.63). In contrast, treated persons who did not achieve SVR had a risk of death that was comparable to those who were never treated, irrespective of type of treatment.

Older persons and those with fibrosis score ≥F3 were at higher risk of dying from liver failure than younger persons and those with a fibrosis score ≤F2. Baseline treatment status was associated with mortality due to liver failure, with a pronounced protective effect for treated persons with SVR (HR, 0.18; 95% CI, 0.08–0.37) but no reduction in risk for persons treated without SVR (HR, 0.78; 95% CI, 0.51–1.18).

For liver cancer, the risk of death was higher for older persons and those with a high fibrosis stage. Having a history of IDU had little impact on liver cancer mortality. Compared with never-treated persons, the risk of dying decreased for treated persons with SVR (HR, 0.33; 95% CI, 0.16–0.71), but not for treated persons without SVR (HR, 1.34; 95% CI, 0.81–2.22).

The risk of dying from nonliver cancer was higher for older persons than for younger persons. Although there was no significant association between nonliver cancer mortality and treatment status, nor with baseline fibrosis score, persons with a history of IDU were more at risk than persons without a history of IDU (HR, 3.22; 95% CI, 1.64–6.33).

Having ever used injectable drugs was associated with an increased risk of dying from unnatural causes (HR, 3.65; 95% CI, 1.67–7.97). In addition, persons aged 20 years were more at risk than persons aged 40 years or older (HR, 2.9; 95% CI, 1.21–6.9), as well as persons with a fibrosis score ≥F3 compared with those with a fibrosis score ≤F2 (HR, 1.91; 95% CI, 1.07–3.4). There was no association between unnatural causes of death and treatment status.

Results from the sensitivity analysis were similar to the main analysis for all-cause mortality, but there were some notable differences for cause-specific mortality (Supplementary Data).

## DISCUSSION

Based on SCCS data, we investigated time trends and risk factors of all-cause and cause-specific mortality among HCV-infected persons in Switzerland. Linkage of LTFU persons to the death registry did not significantly increase the number of deaths. However, the proportion of unknown causes of death decreased substantially after linkage, from 42% to 10%.

Leading causes of death changed over time, with a substantial increase in the proportion of liver cancer–related deaths. Similar to other studies [7], we found that mortality remained stable among HCV-infected persons in Switzerland over the past few years.

The risk of death was lower for women (similar to other studies [12]), younger persons, persons with a lower fibrosis

score, persons without a history of IDU, and treated persons who reached SVR, with a first indication of a more positive effect with DAAs compared with IFN-based treatments. However, in contrast to some other studies, we found little evidence that being treated with failure had a protective effect compared with remaining untreated [22, 23]. For both liver failure and liver cancer, the risk of dying was significantly associated with treatment, with a lower risk for treated persons with SVR than for treated persons without SVR or untreated persons. Having a history of IDU was an important risk factor for death from nonliver cancer and unnatural causes, explained by the inclusion of overdose/accidental poisoning in this category.

Two factors probably explain the change in leading causes of death over time: Increasing age may cause more people to die of liver disease and more people with cirrhosis to develop liver cancer; and ascertainment of cause of death may have improved over time. Indeed, the proportion of unspecified causes of death decreased from 13% in 2008–2013 to 4% in 2014–2016, reflecting the better linkage in the later years (92% of deceased persons in 2014–2016 were linked, compared with 67% in 2008–2013). Furthermore, the declining proportion of liver failure while increasing liver cancer might be due to more extensive ascertainment of small foci of hepato-cellular carcinoma (HCC) over time.

The expected decrease in mortality due to DAA is not occurring, or more probably not yet observable. Indeed, some studies have reported a decline in mortality after the introduction of DAA, but only from 2016 onwards [13]. As data for wider use of DAA were only available for 3 years (2014–2016), a period when prescription of DAA in Switzerland was limited based on fibrosis stage [24–26], we were not able to evaluate the difference between successful IFN treatment and successful DAA treatment regarding liver-related mortality.

Persons who inject drugs (PWID) are a key subgroup of HCV-infected persons in Switzerland and other high-income countries, where most HCV infections occur via IDU [27, 28].

Despite the implementation of the 4-pillar strategy [29–31], a national drug policy in Switzerland since 1994, additional obstacles exist for HCV treatment among PWID both for treatment providers and patients [32]. Consequently, some HCV-infected PWID enter care relatively late, at an advanced fibrosis stage. The proportion of infected PWID who receive anti-HCV treatments (DAA or IFN-based) has increased only slightly, from 51% in 2008–2013 to 58% in 2014–2016. The waiting time to initiate DAA treatment is likely shorter than for IFN-based treatment, and even PWID who enter care late are more likely to reach favorable outcomes with DAAs. However, persons with a history of IDU now have a higher risk of dying from nonliver cancer, potentially related to their addiction and additional risk factors common among PWID, such as smoking or excessive alcohol consumption [33].

Differences between causes of death reported in the SFSO death registry and the SCCS can be partly explained by different coding practices. The main focus of the SCCS was likely to identify all HCV-related deaths, and there was less emphasis on recording the exact cause of death. For 21% of SCCS entries, cause of death was "liver failure" in 1 data set and "liver cancer" in the other, 2 causes that are relatively similar. Overall, clear discrepancies in the causes of death recorded in the SCCS and the SFSO exist in only 21% of cases (Supplementary Data).

To our knowledge, this is one of the first studies investigating detailed risk factors and time trends of cause-specific mortality among HCV-infected persons. Via linkage with the death registry, we significantly improved information on causes of death. By accounting for competing risks, including age as a continuous covariate (and not categorizing it arbitrarily), and adjusting models for time-dependent covariables, we were able to improve the accuracy of our analysis.

A limitation of this study was the unavailability of complete data relating to fibrosis stage evolution. Hence, we made no assumption on fibrosis evolution over time and used multiple imputation to handle missing values, which may compromise the robustness of our analysis. We did a sensitivity analysis using complete cases only. In this analysis, the number of persons for the cause-specific analysis was relatively limited, and results may therefore be less reliable.

In conclusion, although mortality did not (yet) decrease with DAA, we found that causes of death changed over time. With the wider use of DAA, irrespective of fibrosis stage, liver-related mortality will likely continue to decline in the future. Continuous monitoring of mortality and causes of death will therefore remain important to the evaluation of the long-term effect of DAA and to developing effective interventions.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.


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