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Liver-related mortality and hospitalizations attributable to chronic hepatitis C virus coinfection in persons living with HIV

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Abstract
Objectives. The aim of this study was to compare liver-related mortality and liver-related hospitalizations for persons living with HIV (PLWH) with and without hepatitis C virus (HCV) exposure, and to estimate the fraction of liver disease attributable to chronic HCV coinfection.
Methods. An ambispective cohort study followed PLWH between 1993 and 2014. PLWH were classified into three groups: those who were HIV-monoinfected, those who cleared HCV spontaneously and those with chronic HCV coinfection. Liver-related mortality was estimated for the three groups and compared with the adjusted standardized mortality ratio.
Results. Data for 2379 PLWH were included in the study (1390 monoinfected individuals, 146 spontaneous HCV resolvers and 843 with chronic HCV coinfection). Global mortality was 33.8%, 21.4% of which was liver-related. Patients who died from liver-related causes were mostly on antiretroviral therapy and had an undetectable HIV viral load when they died. The liver-related mortality rate in those with chronic HCV coinfection was 10.01 per 1000 patient-years *vs*. 3.84 per 1000 patient-years in the HIV-monoinfected group ($P < 0.001$). The adjusted standardized mortality ratio in the chronically HCV-coinfected group was 4.52 (95% confidence interval 2.98–5.86). The fractions of liver-related mortality and liver-related hospitalizations attributable to chronic HCV coinfection were 0.61 and 0.74, respectively. There were no differences in liver-related events between HIV-monoinfected individuals and those who spontaneously cleared HCV.
Conclusions. Chronic HCV infection increases the risk of liver-related mortality and liver-related hospitalizations in PLWH, despite good control of HIV infection. Sixty per cent of liver-related mortality in chronically HCV-coinfected PLWH could be attributable to chronic HCV infection. The effect of mass HCV eradication with new therapies should be evaluated.

Keywords: hepatitis C virus coinfection, liver-related hospitalization, liver-related mortality, people living with HIV

Introduction

Liver disease is an important contributor to morbidity and mortality among persons living with HIV (PLWH). Liver-related mortality is common in PLWH with chronic hepatitis C virus (HCV) coinfection, accounting for 20–40% of all deaths, and is the main cause of liver-related hospitalizations [1, 2].

In chronically HCV-infected persons without HIV infection, approximately 55–65% of liver-related mortality can be attributed to chronic HCV infection, when compared with persons who spontaneously clear HCV. In many cases, HCV infection is associated with a particular lifestyle profile and, in the general population, spontaneous HCV resolvers are a good benchmark group comparator for evaluation of the independent contribution of chronic HCV infection, because they have the same risk factors and lifestyle as those with chronic HCV infection [3]. In PLWH, the differences between HIV-monoinfected individuals and spontaneous HCV resolvers in terms of liver-related mortality and liver-related hospitalizations are unknown.

The role of hepatitis viruses in the progression of liver damage is unquestionable. However, there are many other factors that contribute to the development of liver injury in PLWH, such as HIV replication, immune dysfunction, opportunistic infections, lifestyle exposures (alcohol or other drugs), metabolic disorders and some antiretroviral agents [4-7]. Sometimes these other factors can be overlooked because of the major role of HCV infection in the progression of liver disease in chronically HCV-coinfected PLWH. The aim of this study was to compare liver-related mortality and liver-related hospitalizations in PLWH with and without HCV exposure and to estimate the fraction of liver disease attributable to chronic HCV coinfection in this population.

Methods

This study included data for all PLWH followed in an ambispective cohort in a reference HIV clinic (University Hospital of A Coruña, Spain) between 1993 and 2014. All hospital admissions and the causes of death were obtained from the hospital records encoded according to the International Classification of Diseases (ICD-9). Liver-related disease was considered to include the following codes: viral hepatitis (070, 573.3), alcoholic liver disease (571.0−571.3), nonalcoholic liver disease (570, 571.4−571.9, 572−573), primary liver cancer (155), and decompensated cirrhosis (789.5, 567.23, 456.0). Cholelithiasis and cholecystitis (574−575) were not included as liver-related conditions. Fatal infections occurring in PLWH with cirrhosis were classified as liver-related deaths/hospitalizations when the episode included a code for cirrhotic decompensation.

Clinical and epidemiological variables were collected and a descriptive analysis was performed for all the variables recorded. PLWH were classified into three groups: those without viral hepatitis [negative for hepatitis B virus (HBV) surface antigen and HCV antibodies], those who spontaneously cleared HCV (HCV antibody-positive and undetectable HCV RNA without anti-HCV therapy) and chronically HCV-coinfected patients. PLWH who received anti-HCV therapy and achieved a sustained viral response (SVR) were excluded; those without an SVR were included in the chronically HCV-coinfected group.

Quantitative variables were reported as mean ± standard deviation (SD) and qualitative variables as frequency and percentage. The three groups were compared using chi-square for qualitative variables and one-way analysis of variance (anova) for quantitative variables.

The liver-related mortality rate was estimated in the three groups (monoinfected individuals, HCV spontaneous resolvers and chronically HCV-coinfected individuals). Liver-related mortality rates were compared using the monoinfected group as the reference, and computing the standardized mortality ratios with their 95% confidence intervals (CIs), adjusted for sex, age at HIV diagnosis and transmission route, using Byar's approximation of the Poisson model. Liver-related hospitalization rates were calculated and compared between groups using the adjusted standardized hospitalization ratios.

The fraction of liver-related mortality attributable to chronic HCV infection was calculated relative to that in monoinfected PLWH using the equation (liver-related mortality rate in chronically HCV-coinfected group – liver-related mortality rate in monoinfected group)/liver-related mortality rate in chronically HCV-coinfected group, and relative to that in spontaneous resolvers as (liver-related mortality rate in chronically HCV-coinfected group – liver-related mortality rate in spontaneous resolvers)/liver-related mortality rate in chronically HCV-coinfected group [3]. The fraction of liver-related hospitalizations attributable to chronic HCV infection was calculated in a similar fashion. Results are expressed with the 95% CI.

Statistical analysis was performed using spss for Windows (v19.0; IBM Corp., Armonk, NY, USA). The research protocol was approved by the Regional Ethics Committee (register code 2015/164).

Results

A total of 2379 PLWH followed between 1993 and 2014 were included in the study, contributing 26 778 patient-years. The cohort included 75.2% men and had a mean (±SD) of 11.9 ± 4.2 years of follow-up. The main characteristics of the three study groups are shown in Table 1. The prevalence of HBV coinfection in chronically HCV-coinfected PLWH was 10.1%. Sixty-four (7.6%) of the 843 chronically HCV-coinfected PLWH had been treated with anti-HCV agents, all of which were interferon (IFN)-based regiments, without achieving SVR. Seventy chronically HCV-coinfected PLWH who were successfully treated with anti-HCV therapy were excluded. The mean (±SD) duration of HCV infection in the chronically HCV-coinfected group was 13.4 ± 4.2 years.

Table 1. Demographic characteristics, hospitalizations and mortality rates among monoinfected people living with HIV (PLWH), PLWH with spontaneous hepatitis C virus (HCV) clearance and PLWH with chronic HCV coinfection

	Monoinfected PLWH	PLWH who were spontaneous resolvers	Chronically HCV-coinfected PLWH	*P*-value
Number of patients	1390	146	843	
Male (%)	77.99	69.86	71.65	0.065
Age at HIV diagnosis (years) [mean ± SD]	34.8 ± 9.6	29.8 ± 10.2	28.4 ± 7.4	0.002
HIV transmission route (%)				< 0.001
IDU	23.96	81.51	83.99	
MSM	42.01	8.90	10.32	
CD4 count nadir (cells/μL) [mean ± SD]	204 ± 102	184 ± 126	163 ± 108	< 0.001
CDC-C (%)	51.9	54.8	59.4	0.002
Total follow-up (patient-years)	13 920	1766	11 092	< 0.001
Liver-related mortality events [*n* (%)]	54 (3.88)	7 (4.79)	111 (13.17)	< 0.001
Non-liver-related mortality events [*n* (%)]	388 (27.91)	40 (27.40)	203 (24.08)	0.134
Liver-related mortality rate (95% CI)a	3.88 (2.99–5.03)	3.96 (1.92–8.16)	10.01 (8.31–12.04)	< 0.001
Non-liver-related mortality rate (95% CI)a	27.87 (25.27–30.74)	22.65 (16.68–30.69)	18.30 (15.97–20.97)	0.140
Liver-related hospitalizations (*n*)	105	15	326	–
Non-liver-related hospitalizations (*n*)	3329	376	2578	–
Liver-related hospitalization rate (95% CI)a	7.54 (6.23–9.12)	8.49 (5.15–13.97)	29.39 (26.41–32.70)	< 0.001
Non-liver-related hospitalization rate (95% CI)a	239.15 (232.14–246.31)	212.91 (194.45–232.62)	232.42 (224.65–240.37)	0.070

CDC-C, Centers for Disease Control and Prevention category C; CI, confidence interval; IDU, injecting drug use; MSM, men who have sex with men; SD, standard deviation.
[a] Per 1000 patient-years.

In the whole cohort of PLWH, all-cause mortality involved 803 individuals (33.8%), including 442 (31.8%) monoinfected individuals, 47 (32.2%) spontaneous HCV resolvers and 314 (37.2%) chronically HCV-coinfected patients. Of these, 78.6% of deaths were secondary to non-liver-related causes; the most common cause of death was AIDS-related (47.7% in the monoinfected group, 48.9% in spontaneous HCV resolvers and 48.1% in the chronically HCV-coinfected group; $P = 0.106$), followed by non-AIDS-related infections (22.8% in the monoinfected group, 19.1% in the spontaneous HCV resolvers and 22.6% in the chronically HCV-coinfected group; $P = 0.060$). The main causes of liver-related mortality in the chronically HCV-coinfected group were liver cancer (34.2%), cirrhotic decompensation (28.8%), nonalcoholic liver disease (18.9%) and alcoholic liver disease (10.8%), whereas in the monoinfected group, they were nonalcoholic liver disease (53.7%), alcoholic liver disease (27.7%), cirrhotic decompensation (11.1%) and liver cancer (5.5%).

The liver mortality rate in each group is shown in Table 1. Compared with the monoinfected group, spontaneous resolvers had similar all-cause mortality (standardized mortality ratio 1.02; 95% Cl: 0.71–1.47), but mortality was higher in the chronically HCV-coinfected group (standardized mortality ratio 1.27; 95% CI: 1.06–1.52). The standardized liver-related mortality ratios are presented in Figure 1.

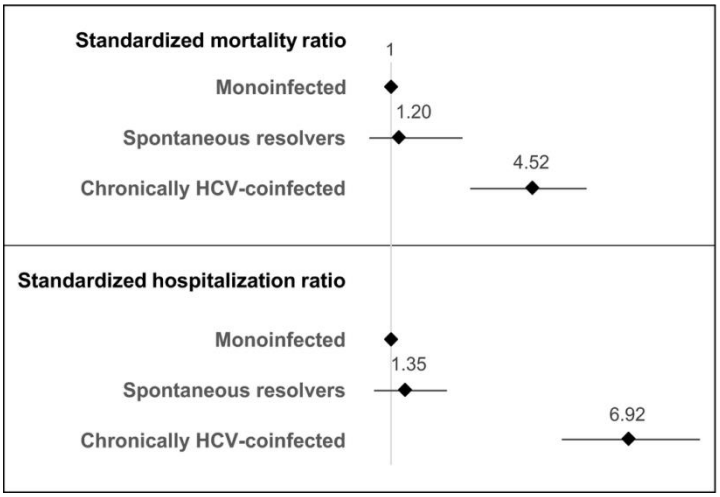

Figure 1. Standardized liver-related mortality ratios and standardized liver-related hospitalization ratios, with monoinfected people living wih HIV (PLWH) as the reference. The ratios have been adjusted by gender, age at HIV diagnosis and transmission route, and are shown with their 95% confidence intervals. HCV, hepatitis C virus.

The mean (±SD) time from HIV diagnosis to non-liver-related death was 8.1 ± 6.4 years in the monoinfected group, 7.6 ± 6.0 in the spontaneous HCV resolvers and 7.9 ± 6.6 in the chronically HCV-coinfected group (P = 0.062). In contrast, the mean (±SD) time from HIV diagnosis to liver-related death was 7.6 ± 6.8 years in the monoinfected group, 7.9 ± 6.1 in the spontaneous HCV resolvers and 13.3 ± 7.1 in the chronically HCV-coinfected group (P = 0.003). Those PLWH who died of liver-related causes were mostly undergoing antiretroviral treatment when they died (87.0% of the monoinfected group, 85.7% of the spontaneous HCV resolvers and 90.0% of the chronically HCV-coinfected group; P = 0.810), and most had controlled HIV replication (< 400 HIV-1 RNA copies/mL) (74.0% of the monoinfected group, 71.0% of the spontaneous HCV resolvers and 76.6% of the chronically HCV-coinfected PLWH).

During the study period, 6729 hospitalizations were recorded (6.6% liver-related) in 1844 patients (77.5% of the whole cohort); the median number of admissions was 2 (range 1–4). The main reasons for hospitalization of monoinfected PLWH were AIDS-related diseases (26.2%), other infections (28.5%) and cardiovascular disease (14.3%) whereas in the chronically HCV-coinfected group they were AIDS-related diseases (24.8%), other infections (27.7%) and liver-related diseases (11.2%). Figure 1 shows the standardized liver-related hospitalization ratios.

There were no differences in liver-related hospitalizations and liver-related mortality between monoinfected PLWH and PLWH who spontaneously cleared HCV. After adjusting for age at HIV diagnosis, sex and transmission route, chronically HCV-coinfected individuals showed a more than fourfold higher rate of liver-related mortality and close to a sevenfold higher rate of liver-related hospitalizations than monoinfected PLWH (P < 0.001), as shown in Figure 1.

The fraction of liver-related mortality attributable to chronic HCV infection in PLWH relative to monoinfected PLWH was 0.61 (95% CI: 0.51–0.70) and that relative to spontaneous resolvers was 0.60 (95% CI: 0.51–0.69). The fraction of liver-related hospitalizations in chronically HCV-coinfected PLWH *vs*. monoinfected PLWH was 0.74 (95% CI: 0.69–0.79) and that *vs*. spontaneous resolvers was 0.71 (95% CI: 0.66–0.76); these were not significantly different (P = 0.102).

Discussion

In this study, more than one-third of deaths and 11% of hospitalizations in chronically HCV-coinfected PLWH were liver-related, as previously documented [8]. After adjustment, chronically HCV-coinfected PLWH had a higher mortality than monoinfected PLWH, mainly bacause of liver-related causes (standardized mortality ratio 6.92). There were no differences in terms of liver events between monoinfected PLWH and those who spontaneously resolved HCV infection. This similarity may be partly explained by their similar lifestyle exposures, despite the lower proportion of injecting drug users in monoinfected PLWH than in spontaneous resolvers and the higher prevalence of other liver and metabolic disorders (such as steatosis) in PLWH, compared with the general population [4]. Therefore, in this population, patients without viral hepatitis could be used as a benchmark group comparator to explore the relative contribution of chronic HCV infection.

To our knowledge, this is the first study estimating the fraction of liver disease in PLWH attributable to chronic HCV infection. These data agree with the opinion that the majority of liver deaths in chronically HCV-coinfected patients are attributable to chronic HCV exposure. The attributable-fraction analysis provides further information: it shows that a significant proportion of liver-related mortality can occur independently of HCV infection, which should be considered when the future impact of treatment for HCV infection is estimated [1, 2]. There are several studies evaluating the role of SVR to HCV treatment in liver disease progression and liver-related mortality in PLWH, most of which were included in a recent meta-analysis [9]. However, these studies were performed during the IFN era when less than one-third of patients elected to have anti-HCV therapy, so the favourable impact of HCV eradication could be maximized, due to selection bias [10]. Survival of PLWH achieving SVR in these classical studies was usually better than that of HCV-uninfected PLWH because of a selection bias. Consequently, more data on treatment and survival with the newer anti-HCV treatments and a more diverse sample population are needed [1].

In case−control studies comparing chronically HCV-infected patients with and without HIV infection, effective HIV control reduced, but did not eliminate, the higher risk of liver disease progression in coinfected patients in terms of hepatic decompensation, fibrosis progression and hepatocellular carcinoma, and was inversely related to the CD4 count [11, 12]. Our study did not include data on the CD4 count at the time of the liver events, but chronically HCV-coinfected PLWH had a lower CD4 nadir than did monoinfected PLWH, despite similar antiretroviral treatment exposure and efficacy in terms of HIV viral load suppression.

This study has some limitations. First, some deaths (such as those attributable to infections in cirrhotic patients, or cancers other than hepatocellular carcinoma in which chronic HCV infection was involved) were coded as non-liver-related disease despite the important contribution of chronic HCV infection. Secondly, some important variables such as alcohol intake and active drug use were not available. Thirdly, PLWH with hepatitis B or D were excluded unless they were chronically HCV-coinfected, and the effect of these hepatitis coinfections on liver-related events was not considered. The impact of anti-HCV treatment and achievement of an SVR were not evaluated. Finally, the immunological status of PLWH was not appropriately recorded.

In conclusion, similar to the general population, close to two-thirds of liver-related mortality in chronically HCV-coinfected PLWH could be attributed to chronic HCV infection, but the liver-related mortality rate in PLWH was double that found in the general population (10.01 *vs.* 5.35 per 1000 patient-years, respectively) [3]. Chronic HCV infection is a relevant problem in PLWH, significantly increasing the rates of morbidity and mortality. Eradication of chronic HCV coinfection is crucial in PLWH, but is probably not a definitive solution to the problem of liver disease, and preventive, educational and social interventions are particularly important in PLWH.

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