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4 **Liver fibrosis and all-cause mortality in chronic HCV-infected diabetic patients:**
5 **a paradoxical association? (ANRS CO22 HEPATHER)**
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41 Patient consent statement

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3 We read with great interest the article published by Ciancio *et al.*, which reported
4 long-term improvement of glycometabolic control in diabetic patients with chronic hepatitis C
5 following sustained virological response with direct-acting antivirals (DAA) (1). They also
6 reported a detrimental effect of baseline diabetes on hepatocellular carcinoma (HCC)
7 incidence in cirrhotic hepatitis C patients after multiple adjustment, and a higher mortality rate
8 in hepatitis C patients with diabetes than in their non-diabetic counterparts. The authors'
9 valuable data regarding the long-term benefits of hepatitis C virus clearance on glucose
10 homeostasis in diabetic patients, highlight the need to confirm: (i) that diabetic hepatitis C
11 patients present a higher risk of all-cause mortality, and (ii) whether specific mortality risk
12 factors should be given particular scrutiny in this sub-population. We might expect that the
13 higher rate of HCC incidence *Ciancio et al.* reported in diabetic HCV patients contributes to a
14 higher all-cause mortality rate, as was previously found before the DAA era (2,3). Diabetes is
15 also a well-known risk factor for cardiovascular disease, although DAA treatment appears to
16 diminish the risk (4).

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19 We aimed to confirm whether diabetes is associated with higher all-cause mortality in
20 chronic HCV-infected patients in the DAA era, and whether specific risk factors affect all-
21 cause mortality differently in patients with and without diabetes. Our analyses were based on
22 longitudinal data from ANRS CO22 HEPATHER, a national, multicenter, prospective cohort
23 study conducted in France, which collected annual clinical and socio-behavioral data over
24 five years of follow-up in chronic HCV-infected patients who were not on treatment at
25 inclusion (5). Unlike *Ciancio et al.*'s study, no fibrosis stage inclusion criterion was set. We
26 used a Cox proportional hazards model to investigate the association between diabetes and
27 all-cause mortality, as well as the potential role of other covariates on all-cause mortality,
28 using analyses stratified by diabetes status (i.e., diabetic/not diabetic) at baseline. All
29 covariates were measured at baseline, except for HCV cure, which was considered a time-
30 varying variable.

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33 Of the 10 364 participants included, 13.7% (n=1419) had diabetes at baseline, and
34 82.6% (n=8557) were HCV-cured by the end of follow-up. Median time since HCV diagnosis
35 was between 14 and 15 years. Six hundred and ninety-seven deaths occurred in the study
36 population over 37 633.7 person-years, including 160 diabetic patients. For the whole
37 sample, the all-cause mortality rate was 1.85/100 person-years (95% confidence interval [CI],
38 1.72-1.99), specifically 3.14/100 person-years (95% CI, 2.69-3.67) in diabetic patients, and
39 1.65/100 person-years (95% CI, 1.52-1.80) in non-diabetic patients, corresponding to a
40 hazard ratio (HR) of 1.91 [95% CI, 1.60 – 2.28] for diabetes status ($p < 10^{-3}$).

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43 In multivariable stratified analyses, male gender, older age, being underweight, not
44 HCV cured, and advanced liver fibrosis at baseline (assessed by a FIB-4 score > 3.25 (6))

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3 were all associated with increased mortality in both sub-populations (**Table 1**). Current
4 tobacco smoking, daily coffee intake, an educational level less than high-school diploma, and
5 elevated blood pressure were all independently associated with increased mortality in non-
6 diabetic patients only. The risk of all all-cause mortality associated with having advanced
7 liver fibrosis was two times higher in non-diabetic patients than in diabetic patients (adjusted
8 HR: 5.54 [95% CI, 4.51 – 6.81] *versus* 2.16 [95% CI, 1.51 – 3.09]).
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13 Our results confirm that diabetes is a significant risk factor for all-cause mortality in
14 chronic HCV patients. While Ciancio *et al.* found that a higher risk of HCC incidence was
15 associated with diabetes in cirrhotic HCV patients, we found that the risk of all-cause
16 mortality associated with having advanced liver fibrosis was two times higher in non-diabetic
17 patients than in diabetic patients. These findings may appear paradoxical.
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21 The relatively lower risk of death associated with advanced liver fibrosis in diabetic
22 patients suggests that non-liver-related deaths may also heavily weigh on all-cause mortality
23 in this sub-population, and that the benefits of DAA treatments on glycometabolic control
24 may not be sufficient to counteract the cardiovascular consequences of diabetes as a major
25 cardiovascular risk factor. While a lower hemoglobin A1c level has been associated with
26 lower cardiovascular-related mortality in the general population (7), the fact that more than
27 80% of our study population was over 50, together with the relatively recent arrival of DAA
28 treatments, may mean that the long duration of diabetes in our study sample counteracted
29 the effects which recent improvements in glucose homeostasis have had on cardiovascular
30 events (8). As diabetes is considered a cofactor for liver disease, the lower adjusted hazard
31 ratio for advanced fibrosis in diabetic HCV patients which we found may also be partly due to
32 closer clinical follow-up which focuses on the prevention of liver disease in this sub-
33 population (9). Additionally, this result must be interpreted in the context of the higher all-
34 cause mortality of diabetic patients than their non-diabetic counterparts.
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44 Further studies investigating cause-specific mortality in diabetic and non-diabetic
45 HCV patients in the DAA era need to be conducted, in order to shed light on the respective
46 major risk factors for mortality in these two sub-populations, and adapt their clinical follow-up
47 accordingly.
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Table 1: Factors associated with all-cause mortality (Cox proportional hazards models), multivariable analyses stratified on diabetes status at baseline: the ANRS CO22 HEPATHER cohort (N = 10 364 patients)

	Whole population (N = 10 364)		Multivariable analyses			
	Non-diabetic patients (N = 8945)	Diabetic patients (N = 1419)	Non-diabetic patients (N = 8129)		Diabetic patients (N = 1309)	
	N (%)	N (%)	aHR [95% CI]	P-value	aHR [95% CI]	P-value
Gender						
Female	4 063 (45.4%)	515 (36.3%)	0.48 [0.39 – 0.59]	< 10 ⁻³	0.59 [0.40 – 0.86]	0.007
Male	4 882 (54.6%)	904 (63.7%)	1		1	
Age (years)						
< 50	2 330 (26.1%)	173 (12.2%)	1		1	
50 – 69	5 515 (61.7%)	946 (66.7%)	2.16 [1.61 – 2.89]	< 10 ⁻³	2.61 [1.04 – 6.58]	0.041
≥ 70	1 100 (12.3%)	300 (21.1%)	3.87 [2.70 – 5.55]	< 10 ⁻³	4.28 [1.58 – 11.57]	0.004
HCV genotype						
1	5 758 (64.4%)	897 (63.2%)				
2/4	1 66 (18.6%)	345 (24.3%)				
3/5/6/7	1 401 (15.7%)	159 (11.2%)				
Missing	120 (1.3%)	18 (1.3%)				
Body mass index (kg.m⁻²)						
Underweight (<18.5)	329 (3.7%)	20 (1.4%)	1.60 [1.03 – 2.49]	0.036	2.80 [1.04 – 7.54]	0.042
Normal (≥ 18.5 and < 25)	4 772 (53.3%)	472 (33.3%)	1		1	
Overweight (≥ 25 and < 30)	2 756 (30.8%)	536 (37.8%)	0.92 [0.75 – 1.13]	0.442	0.78 [0.52 – 1.18]	0.239
Obese (> 30)	1 014 (11.3%)	379 (26.7%)	1.02 [0.76 – 1.38]	0.877	1.00 [0.64 – 1.57]	0.984
Missing data	74 (0.8%)	12 (0.9%)				
Years since HCV diagnosis						
Median [IQR]	14.3 [6.8 – 20.0]	14.77 [8.2 – 20.2]				
Alcohol use^a						
Abstinent with past unhealthy use	1 309 (14.6%)	248 (17.5%)				
Abstinent without past unhealthy use	3 587 (40.1%)	692 (48.8%)				
Moderate use	3 574 (40.0%)	422 (29.7%)				

Unhealthy use	422 (4.7%)	44 (3.1%)				
<i>Missing data</i>	53 (0.6%)	13 (0.9%)				
Tobacco smoking						
Never	3 128 (35.0%)	583 (41.1%)	1		1	
Past	2 342 (26.2%)	444 (31.3%)	0.98 [0.76 – 1.27]	0.899	1.07 [0.71 – 1.62]	0.740
Current	3 460 (38.7%)	392 (27.6%)	1.79 [1.39 – 2.31]	< 10 ⁻³	1.31 [0.84 – 2.06]	0.238
<i>Missing data</i>	15 (0.2%)	0				
HCV transmission category						
IDU	2 488 (27.8%)	244 (17.2%)				
Transfusion	2 588 (28.9%)	467 (32.9%)				
Other	1 554 (17.4%)	277 (19.5%)				
<i>Missing</i>	2 315 (25.9%)	431 (30.4%)				
Educational level						
< high-school diploma	4 687 (52.4%)	859 (60.5%)	1		1	
≥ high-school diploma	4 122 (46.1%)	537 (37.8%)	0.71 [0.59 – 0.86]	0.001	1.01 [0.70 – 1.45]	0.961
<i>Missing data</i>	136 (1.5%)	23 (1.6%)				
HCV treatment status^b						
Not cured	1 571 (17.6%)	236 (16.6%)	1		1	
Cured	7 374 (82.4%)	1 183 (83.4%)	0.26 [0.21 – 0.31]	< 10 ⁻³	0.31 [0.22 – 0.44]	< 10 ⁻³
Advanced liver fibrosis						
No (FIB-4 ≤ 3.25)	6 355 (71.1%)	800 (56.4%)	1		1	
Yes (FIB-4 > 3.25)	2 028 (22.7%)	560 (39.5%)	5.54 [4.51 – 6.81]	< 10 ⁻³	2.16 [1.51 – 3.09]	< 10 ⁻³
<i>Missing data</i>	562 (6.3%)	59 (4.2%)				
Coffee consumption						
0 cup/day	2 524 (28.2%)	419 (29.5%)	1		1	
≥ 1 cup/day	6 266 (70.1%)	965 (68.0%)	0.77 [0.63 – 0.93]	0.007	1.23 [0.84 – 1.81]	0.286
<i>Missing data</i>	155 (1.7%)	35 (2.5%)				
Elevated blood pressure or related treatments						
No	6 674 (74.6%)	615 (43.3%)	1		1	

Yes	2 263 (25.3%)	802 (56.5%)	1.53 [1.25 – 1.87]	< 10 ⁻³	1.36 [0.94 – 1.98]	0.106
<i>Missing data</i>	8 (0.1%)	2 (0.1%)				

Variables with a P-value < 0.20 (Wald test) in the univariable analyses were tested in the multivariable model. The final multivariable model was built using a backward selection of variables). All variables with a P-value < 0.05 in either sub-population was kept in the final model for both sub-populations. Analyses were performed using Stata/SE 14.2 software for Windows (StataCorp LP, College Station, TX).

^a Unhealthy alcohol use was defined as >2 and >3 drinks a day for women and men, respectively.

^b HCV cure was the only time-varying variable, N (%) are given at the end of the follow-up aHR, adjusted hazard ratio; CI, confidence interval; IDU, injecting drug use; IQR, interquartile range

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