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## **Liver fibrosis and all-cause mortality in chronic HCV-infected diabetic patients: A paradoxical association? (ANRS CO22 HEPATHER)**

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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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7 Tangui Barré<sup>1</sup>, Clémence Ramier<sup>1</sup>, Vincent Di Beo<sup>1</sup>, Fabrice Carrat<sup>2,3</sup>, Hélène  
8 Fontaine<sup>4,5</sup>, Fabienne Marcellin<sup>1</sup>, Patrizia Carrieri<sup>1#</sup>, Stanislas Pol<sup>2</sup>, Camelia Protopopescu<sup>1</sup>  
9 on behalf of the ANRS/AFEF Hepather study group  
10  
11

12 <sup>1</sup>Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Economiques & Sociales de la  
13 Santé & Traitement de l'Information Médicale, Marseille, France  
14

15 <sup>2</sup>Sorbonne Université, Institut National de la Santé et de la Recherche Médicale (INSERM),  
16 Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France  
17  
18

19 <sup>3</sup>Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Saint-Antoine, Unité de Santé  
20 Publique, Paris, France  
21  
22

23 <sup>4</sup>AP-HP, Hôpital Cochin, Département d'Hépatologie, Paris, France  
24  
25

26 <sup>5</sup>INSERM U1223, Institut Pasteur; Université Paris Descartes, Paris, France  
27  
28

29 <sup>6</sup>Université de Paris ; AP-HP, Hôpital Cochin, Département d'Hépatologie; INSERM U1223,  
30 Institut Pasteur, Paris, France  
31  
32

33  
34  
35  
36 #Corresponding author  
37  
38

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31 Written informed consent was obtained from each cohort participant before enrolment. The  
32  
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34  
35 biomedical research, and was approved by the 'Comité de Protection des Personnes (CPP)  
36  
37 Ile de France 3' Ethics Committee (Paris, France) and the French Regulatory Authority  
38  
39 (ANSM).  
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## 41 42 Patient consent statement

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45 Written informed consent was obtained from each cohort participant before enrolment.  
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## 48 49 Permission to reproduce material from other sources

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53 There is no material from other sources.  
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## ANRS-AFEF Hepather study group

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1  
2  
3 Dofföel, Catherine Mutter, Pauline Simo-Noumbissie (Hôpitaux Universitaires de Strasbourg,  
4 Strasbourg, France), Hélène Barraud, Mouni Bensenane, Abdelbasset Nani, Sarah Hassani-  
5 Nani (CHU de Nancy, Vandoeuvre-lès-Nancy, France), Marie-Albertine Bernard (CHU de  
6 Nancy, Vandoeuvre-lès-Nancy, France and Centre Hospitalier Régional, Metz, France),  
7  
8 Michael Bismuth, Ludovic Caillo, Stéphanie Faure, Georges-Philippe Pageaux, Marie Pierre  
9  
10 Ripault (Hôpital Saint Eloi, Montpellier, France), Karl Barange, Christophe Bureau, Jean  
11  
12 Marie Peron, Marie Angèle Robic, Léa Tarallo (CHU Purpan, Toulouse, France), Marine  
13  
14 Faure, Bruno Froissart, Marie-Noelle Hilleret, Vincent Leroy (CHU de Grenoble, Grenoble,  
15  
16 France), Odile Gorla, Victorien Grard, Hélène Montialoux (CHU Charles Nicolle, Rouen,  
17  
18 France), Muriel François, Christian Ouedraogo, Christelle Pauleau, Anne Varault (Hôpital  
19  
20 Henri Mondor, Créteil, France), Tony Andreani, Bénédicte Angoulevant, Azeline Chevance,  
21  
22 Lawrence Serfaty (Hôpital Saint-Antoine, Paris, France), Teresa Antonini, Audrey Coilly,  
23  
24 Jean-Charles Duclos Vallée, Mariagrazia Tateo (Hôpital Paul Brousse, Villejuif, France),  
25  
26 Armand Abergel, Corinne Bonny, Chanteranne Brigitte, Géraldine Lamblin, Léon Muti  
27  
28 (Hôpital Estaing, Clermont-Ferrand, France), Abdenour Babouri, Virginie Filipe (Centre  
29  
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31  
32 Soraya Merbah (Centre Hospitalier Intercommunal, Créteil, France), Paul Carrier, Maryline  
33  
34 Debette-Gratien, Jérémie Jacques (CHU Limoges, Limoges, France), Florent Artu, Valérie  
35  
36 Canva, Sébastien Dharancy, Alexandre Louvet (CHRU Claude Huriez, Lille, France), Marc  
37  
38 Bardou, Donya Da Costa Souhiel, Patrick Hillon, Marianne Latournerie (Dijon University  
39  
40 Hospital, Dijon, France), Yannick Bacq, Didier Barbereau, Charlotte Nicolas (CHU  
41  
42 Trousseau, 37044 Tours, France), Nisserine Ben Amara, Danièle Botta-Fridlund, Isabelle  
43  
44 Portal (CHU Timone, Marseille, France), Moana Gelu-Simeon, Marie-Josée Lafrance (CHU  
45  
46 de Pointe-à-Pitre, Pointe-à-Pitre, Guadeloupe).  
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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
<b>Gender</b>						
Female	4 063 (45.4%)	515 (36.3%)	0.48 [0.39 – 0.59]	< 10 <sup>-3</sup>	0.59 [0.40 – 0.86]	0.007
Male	4 882 (54.6%)	904 (63.7%)	1		1	
<b>Age (years)</b>						
< 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 <sup>-3</sup>	2.61 [1.04 – 6.58]	0.041
≥ 70	1 100 (12.3%)	300 (21.1%)	3.87 [2.70 – 5.55]	< 10 <sup>-3</sup>	4.28 [1.58 – 11.57]	0.004
<b>HCV genotype</b>						
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%)				
<b>Body mass index (kg.m<sup>-2</sup>)</b>						
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%)				
<b>Years since HCV diagnosis</b>						
Median [IQR]	14.3 [6.8 – 20.0]	14.77 [8.2 – 20.2]				
<b>Alcohol use<sup>a</sup></b>						
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%)				
<b>Tobacco smoking</b>						
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 <sup>-3</sup>	1.31 [0.84 – 2.06]	0.238
<i>Missing data</i>	15 (0.2%)	0				
<b>HCV transmission category</b>						
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%)				
<b>Educational level</b>						
< 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%)				
<b>HCV treatment status<sup>b</sup></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 <sup>-3</sup>	0.31 [0.22 – 0.44]	< 10 <sup>-3</sup>
<b>Advanced liver fibrosis</b>						
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 <sup>-3</sup>	2.16 [1.51 – 3.09]	< 10 <sup>-3</sup>
<i>Missing data</i>	562 (6.3%)	59 (4.2%)				
<b>Coffee consumption</b>						
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%)				
<b>Elevated blood pressure or related treatments</b>						
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 <sup>-3</sup>	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).

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

<sup>b</sup> 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

For Peer Review