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Impact of gender and menopausal status on metabolic parameters in chronic hepatitis C infection

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SUMMARY

Hepatitis C infection (HCV) and menopause are associated with insulin resistance (IR), and IR accelerates HCV-induced liver disease. The relationship between menopause and IR has not been studied in this population. This study aimed to assess the impact of menopause on IR and metabolic syndrome in HCV. One hundred and three (69 men, 16 premenopausal, 18 postmenopausal women) noncirrhotic, nondiabetic HCV-infected adults underwent IR measurement via steady-state plasma glucose during a 240-min insulin suppression test. Metabolic syndrome was defined by at least three of five standard laboratory/clinical criteria. The patient characteristics were as follows: mean age 48 years, waist circumference 94.4 ± 12.4 cm and 37.9% Caucasian. SSPG was higher in postmenopausal than premenopausal women or men (mean difference 18, 95% CI −41 to 76 and 35, 95% CI −3 to 72 mg/dL; respectively). After adjusting for waist circumference, female gender, nonwhite race and triglycerides were positively associated and high-density lipoprotein negatively associated with steady-state plasma glucose. Compared to men, both pre-(Coef 48, 95% CI 12–84) and postmenopausal women (Coef 49, 95% CI 17–82) had higher steady-state plasma glucose. Compared to premenopausal women, men (OR 2.0, 95% CI 0.38–10.2) and postmenopausal women (OR 2.9, 95% CI 0.46–18.8) had higher odds of metabolic syndrome, but this was statistically nonsignificant. Both liver inflammation (OR 7.9) and nonwhite race (OR 6.9) were associated with metabolic syndrome. We conclude that women are at increased risk for IR in HCV. There may also be an increased risk of metabolic syndrome postmenopause. Along with lifestyle modification and weight loss, women with metabolic abnormalities represent an especially at-risk group warranting HCV treatment to prevent adverse metabolic outcomes.

Keywords

hepatitis C infection; insulin resistance; liver inflammation; menopause; metabolic syndrome

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Hepatitis C infection (HCV) is one of the leading causes of chronic liver disease worldwide, affecting up to 160 million individuals [1]. Epidemiologic studies have shown an association between chronic hepatitis C infection (CHC) and insulin resistance (IR) as well as type 2 diabetes mellitus [2–4]. Among patients with CHC, those with IR and/or diabetes have higher rates of progression of liver disease [5] and increased risk of hepatocellular carcinoma (HCC) [6]. IR is also a risk factor for metabolic syndrome (MetS), but despite CHC's association with IR, limited data suggest that the prevalence of MetS does not appear to be increased in CHC [7]. We have previously shown that in patients with CHC infection, women are at particularly higher risk of IR when using direct measurements [8]. However, the relationship between female gender and metabolic abnormalities within the context of CHC has not been previously fully explored.

Women of reproductive age in general are known to have a lower incidence of metabolic abnormalities than men [9], but this sex differential decreases sharply when women reach menopause [10]. Indeed, postmenopausal status is associated with a higher incidence of IR [11,12] and MetS [10,13,14]. This has been attributed to a decrease in oestrogen levels that occurs with onset of menopause, leading to shifts in body weight from peripheral to central adiposity [15–17]. With respect to HCV-induced liver disease, although women have a slower rate of disease progression than men [18–20], liver fibrosis increases following menopause with rates comparable to men [19,21]. In addition, there are higher rates of fibrosis progression and greater histological activity in postmenopausal women when compared with premenopausal women [21–23].

Given that both menopausal status and IR are associated with negative liver disease clinical outcomes, understanding the relationship between menopausal status and metabolic abnormalities is critical to HCV management. This information will help to better identify at-risk individuals for targeted interventions to prevent liver disease progression and those who would most benefit from costly but highly effective anti-HCV therapies. In this study, we aim to assess the impact of menopause on directly measured insulin resistance as well as its clinical consequence, namely metabolic syndrome, in the nondiabetic HCV population.

METHODS

Study population

Noncirrhotic, nondiabetic men and women with chronic hepatitis C aged 18 and above were recruited from San Francisco General Hospital (SFGH) and affiliated clinics at the University of California, San Francisco (UCSF) from 2002 to 2012. Hepatitis C status was confirmed by the presence of both HCV antibody and detectable hepatitis C viral load. Nondiabetic status was initially assessed by a lack of history of diabetes or use of antidiabetic agents and a fasting glucose <126 mg/dL and then confirmed by a 2-h fasting glucose <200 mg/dL during a 75 g oral glucose tolerance test [24]. Exclusion criteria were the presence or known history of cirrhosis, hepatitis B or HIV co-infection, liver disease other than HCV, prior HCV treatment, steroid or anabolic therapy, or medical conditions influencing study participation. This study was approved by the UCSF Committee on Human Research and subjects provided written informed consent.

Study procedures

Participants underwent a medical interview (including menopause status defined as no menstrual period for at least 12 months) [25], physical examination and laboratory evaluation. Some patients also underwent a liver biopsy as part of standard of care. Liver histological evaluation was performed by a pathologist blinded to the patient's metabolic profile using the Ludwig–Batts scoring system [26]. Body mass index (BMI) was categorized as normal (<25 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥30 kg/m^2). Metabolic syndrome was defined by the presence of at least three of the five standard criteria including high waist circumference, blood pressure, fasting glucose, triglycerides and low high-density lipoprotein (HDL) [27]. Subjects were admitted to the UCSF Clinical and Translational Science Institute Clinical Research Center (CRC) for study tests.

Metabolic testing

At baseline, patients underwent a 2-day inpatient hospital admission. On day one, a 75-g oral glucose tolerance test (OGTT) was performed after an overnight 12 h fast. On day two, following another overnight 12 h fast, each subject underwent the modified 240-min insulin suppression test (IST) [8]. During this test, higher steady-state plasma glucose (SSPG) levels represent higher degrees of insulin resistance.

Statistical analyses

Descriptive analyses were summarized using mean ± SD or median (range) for continuous variables and using frequencies and percentages for categorical variables overall and by gender and menopausal status. Patient and viral characteristics were compared by menopausal status using Kruskal–Wallis tests for continuous variables for omnibus comparisons, *t*-tests for pairwise comparisons of means and chi-squared tests for categorical variables. Univariate and multivariate linear regression modelling was used to assess the relationship between menopause and SSPG, while controlling for other factors, and logistic regression was used for MetS. Statistical significance was defined as a *P*-value <0.05 (two-sided). All analyses were performed using STATA version 12.0 (STATA Corporation, College Station, TX, USA) or SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

One hundred and three noncirrhotic, nondiabetic men (*n* = 69) and women (*n* = 34) who met the inclusion criteria were included in the data analysis. Women were further classified as premenopausal (*n* = 16) or postmenopausal (*n* = 18), and approximately half (53%) of the female subjects were postmenopausal. Table 1 summarizes the patient characteristics overall and by gender and menopausal status. While there were no statistically significant differences in race/ethnicity distribution between men and women, as expected, the mean age for postmenopausal women was significantly higher than premenopausal women and men. In addition, a higher proportion of postmenopausal women were obese and had high waist circumference compared to premenopausal women (61% *vs* 44%, *P* = 0.31) and also men (61% *vs* 22%, *P* = 0.0012). Moreover, a significantly higher proportion of men reported heavy alcohol use compared to women. HCV duration was longer in postmenopausal women reflective of the older age of patients in this category, but other viral factors were

similar between women and men. Among those with liver biopsy (n = 80), a higher degree of fibrosis and steatosis was noted in postmenopausal women compared with premenopausal women and men; these did not reach statistical significance.

Menopause and metabolic parameters

With respect to lipid parameters, both pre- and postmenopausal women had higher HDL levels than men (Table 1). The overall mean SSPG levels were 152, 115 and 108 mg/dL in postmenopausal women, premenopausal women and men, respectively (Fig. 1). The SSPG levels in postmenopausal women were higher than premenopausal women (mean difference 18, 95% CI −41 to 76 mg/dL, P = 0.6) and men (mean difference 35, 95% CI −3 to 72 mg/dL, P = 0.07). We further explored the relationship between SSPG and BMI or waist circumference by gender and menopausal status (Figs 2a,b). An increase in SSPG was seen in all groups with rising BMI and waist circumference irrespective of gender and menopausal status, but premenopausal women seemed to have greater increases in SSPG with increasing BMI and waist circumference than postmenopausal women or men, although the interaction terms for this did not approach statistical significance in multivariate models (P > 0.7). With respect to metabolic syndrome, the prevalence of metabolic syndrome was higher in postmenopausal women compared to premenopausal women and men (27.8% *vs* 12.5% *vs* 17.4%, P = 0.48), although this was not statistically significant.

Influence of menopause status on insulin resistance (SSPG)—On multivariate analysis (Table 2) when adjusting for waist circumference, female gender, nonwhite race and triglyceride levels were positively associated, and HDL levels negatively associated, with SSPG. Compared to men, both pre- (Coef 48, 95% CI 12 to 84, P = 0.009) and postmenopausal women (Coef 49, 95% CI 17 to 82, P = 0.0029) had higher SSPG levels, and these estimates did not change substantially when further adjusting for age or family history of diabetes (data not shown). However, among women, menopausal status had little independent association with SSPG levels (Coef 1, 95% CI −42 to 44 mg/dL, P = 1.0) when controlling for waist circumference. This finding also persisted when controlling for age (Coef 9, 95% CI −42 to 59, P = 0.73). In a subset of patients who had undergone a liver biopsy, once again women had higher SSPG levels compared to men when controlling for waist circumference, and HCV-induced liver inflammation on histology was also positively associated with SSPG (Coef 38, 95% CI 10 to 66, P = 0.009). We further explored whether an interaction between waist circumference and menopausal status influenced SSPG levels, but we did not find evidence for such an interaction (P = 0.89).

Influence of menopausal status on metabolic syndrome—On univariate analysis, postmenopausal women (OR 2.7, 95% CI 0.4 to 16.4, P = 0.28) and men (OR 1.5, 95% CI 0.3 to 7.4, P = 0.64) had statistically nonsignificant higher odds of MetS compared to premenopausal women. On multivariate analysis that included menopausal status, nonwhite race was the only statistically significant independent predictor of higher rates of MetS (OR 6.9, 95% CI 1.5 to 32.0, P = 0.014) (Table 3). However, compared to men, postmenopausal women had a higher odds (OR 1.5, 95% CI 0.4 to 5.3, P = 0.52), and premenopausal women had a lower odds (OR 0.51, 95% CI 0.10 to 2.6, P = 0.42) of MetS, although neither reached

statistical significance. Controlling for age did not make a substantial difference in the odds ratios associated with menopause category (data not shown). Compared to premenopausal women, men (OR 2.0, 95% CI 0.38 to 10.2, $P = 0.42$) and postmenopausal women (OR 2.9, 95% CI 0.46 to 18.8, $P = 0.25$) had two to three times higher odds of MetS. In the subcategory of patients with liver biopsy, HCV-induced liver inflammation was positively associated with higher odds of MetS independent of menopausal status (OR 7.9, 95% CI 1.5 to 43.2, $P = 0.017$).

DISCUSSION

To our knowledge, this is the first study to describe the impact of menopause on directly measured insulin resistance as well as metabolic syndrome in the hepatitis C population. In this nondiabetic and noncirrhotic cohort, postmenopausal women had a higher rate of obesity compared to both men and premenopausal women. Although female gender overall was associated with higher SSPG levels, menopause status was not an independent predictor of SSPG when controlling for waist circumference. However, compared to premenopausal women, male gender and postmenopausal status were associated with two to three times higher rates of metabolic syndrome. Importantly, independent of gender or menopausal status, HCV-induced liver inflammation was associated both with insulin resistance and higher odds of metabolic syndrome.

Our finding of an association between postmenopausal status and higher BMI and waist circumference in women and also compared to men has previously been shown in the non-HCV population [10,28]. The increase in central body adiposity after menopause is a risk factor for insulin resistance, diabetes and cardiovascular disease, independent of total body adiposity [29,30]. Similarly, in this HCV cohort, higher waist circumference was positively associated with SSPG levels. Moreover, SSPG was associated with increasing triglycerides and lower HDL levels; factors that in addition to waist circumference comprise the metabolic syndrome phenotype and increase the risk for cardiovascular disease, diabetes [27,31–33] and nonalcoholic fatty liver disease (NAFLD) [34–36].

In the general population, male gender poses an increased risk for insulin resistance and diabetes compared to women [11,37–39], but this protective effect of female gender decreases with age, particularly in woman above age 50, an age that is considered the average age for menopause onset [11]. In contrast to the general population, we have previously shown that female gender was associated with directly measured insulin resistance (SSPG) in the setting of HCV infection [8]. However, this association does not appear to be influenced by menopausal status *per se* after accounting for other factors. On the other hand, similar to other studies, HCV-induced moderate-to-severe liver inflammation was significantly associated with insulin resistance [4] as well as a sevenfold higher odds of metabolic syndrome independent of gender or menopausal status. This suggests that in HCV, an infection that itself increases the risk of insulin resistance, the complex interplay between virus and host may influence the gender effect on insulin resistance parameters in a way that differs from the non-HCV population. Yet, moderate-to-severe liver inflammation appears to be consistently associated with adverse metabolic consequences in men and women in HCV.

Metabolic syndrome is highly prevalent in the US population, but the prevalence varies by age, ethnicity, gender, the definition used, as well as the population studied [40]. Because the definition of metabolic syndrome relies on a threshold of three of five features, the prevalence estimates do not necessarily differentiate between various combinations of metabolic syndrome component subtypes. Nevertheless, similar to the general population and that observed with SSPG, nonwhite race (predominantly African Americans and Latinos) was associated with metabolic syndrome in this HCV cohort [32,41,42]. With respect to gender, studies have shown that in the general population, men have earlier onset and increased rates of metabolic syndrome than women [42–44], a difference that decreases sharply after women reach menopause [10,45]. Moreover, a recent study of the Third National Health and Nutrition Survey in the United States showed that abdominal obesity was the dominant component of metabolic syndrome in women, whereas risk factor combinations were more variable in men [46]. In our study, premenopausal women had lower odds and postmenopausal women had higher odds of metabolic syndrome compared to men, although these findings did not reach statistical significance. Moreover, consistent with prior findings [10,13,14,45], postmenopausal women had about three times higher odds of metabolic syndrome compared to premenopausal women. These results suggest that certain components of metabolic syndrome, namely waist circumference, that were highest in our postmenopausal women may also be a critical driver of metabolic syndrome in HCV infection.

This study significantly contributes to our understanding of the influence of gender and menopause on insulin resistance in a large cohort of HCV-infected individuals with detailed metabolic characterization including directly measured insulin resistance. Although a larger sample size may provide additional insight, performing direct measurements of insulin sensitivity is logistically impractical in larger patient cohorts. While our sample size provided useful precision for estimating factors that influence insulin resistance due to the accuracy of the insulin suppression test [47], our confidence intervals for the odds ratios for metabolic syndrome by menopausal status were very wide, providing little evidence against potentially important associations.

In summary, women in general are at increased risk for insulin resistance in HCV compared to men, and we found some evidence that postmenopausal status increases the risk of metabolic syndrome. In this era of highly effective direct acting anti-HCV therapy [48,49], prevention of adverse metabolic consequences associated with HCV may be achieved by either providing HCV treatment or implementing preventative metabolic screening measures for those at highest risk. As access to HCV therapy is currently prioritized mainly based on liver disease severity due to high cost, women and ethnic minorities with metabolic abnormalities may be an especially at-risk population warranting HCV treatment as a strategy to prevent adverse metabolic outcomes, in addition to life style modification and weight loss.

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Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CHC	chronic hepatitis C
Coef	coefficient
HCC	hepatocellular carcinoma
HCV	hepatitis C infection
HDL	high-density lipoprotein
IR	insulin resistance
IST	insulin suppression test
kg	kilogram
MetS	metabolic syndrome
m	metre
NAFLD	nonalcoholic fatty liver disease
OGTT	oral glucose tolerance test
SD	standard deviation
SFGH	San Francisco General Hospital
SSPG	steady-state plasma glucose
TG	triglyceride
UCSF	University of California San Francisco

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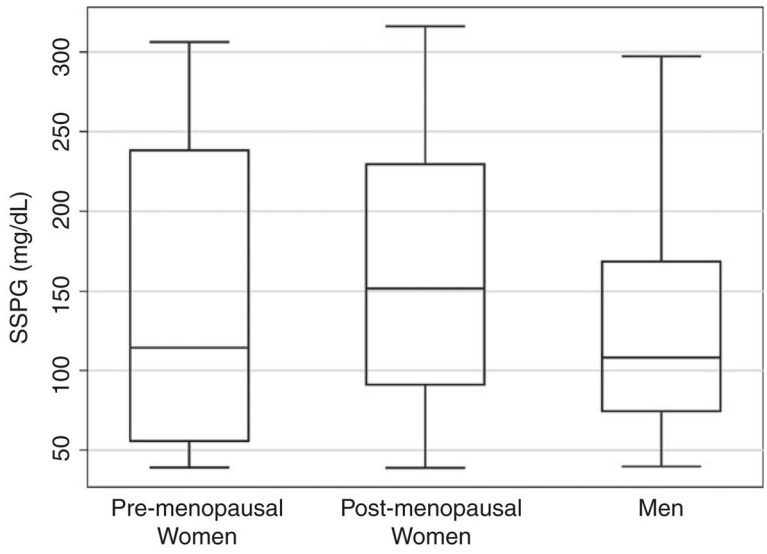

Fig. 1.

Box plots of SSPG levels (mg/dL) categorized by gender and menopausal status. The line represents the median SSPG value, the box represents the 25th and 75th percentiles, and the ends of the whiskers represent the minimum and maximum value of SSPG.

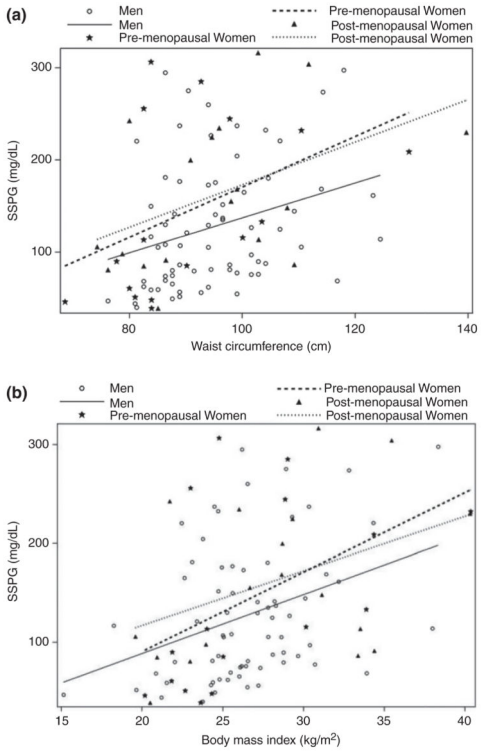

Fig. 2.

(a) Association of SSPG with waist circumference according to gender and menopause category. (b) Association of SSPG with body mass index according to gender and menopause category.

Table 1

Host and viral characteristics by gender and menopausal status

Patient characteristics	Total *n* = 103	Men *n* = 69	Premenopausal Women *n* = 16	Postmenopausal Women *n* = 18	*P*-value*
Age (mean ± SD), years	48.1 ± 6.8	48.0 ± 6.2	42.8 ± 7.5	53.1 ± 4.71	**0.0002**
Race/Ethnicity, *n* (%)					
Caucasian	39 (37.9)	30 (43.5)	4 (25.0)	5 (27.8)	0.22
African American	19 (18.4)	15 (21.7)	1 (6.3)	3 (16.7)	
Latino	39 (37.9)	20 (29.0)	10 (62.5)	9 (50)	
Other	6 (5.8)	4 (5.8)	1 (6.3)	1 (5.6)	
Body mass index category (kg/m^2), *n* (%)					
Normal (<25)	38 (36.9)	23 (33.3)	9 (56.3)	6 (33.3)	**0.029**
Overweight (25–30)	44 (42.7)	36 (52.2)	3 (18.8)	5 (27.8)	
Obese (>30)	21 (20.4)	10 (14.5)	4 (25)	7 (38.9)	
High waist circumference, *n* (%)	33 (32.0)	15 (21.7)	7 (43.8)	11 (61.1)	**0.0034**
Current alcohol use, *n* (%)	37 (35.9)	21 (30.4)	5 (31.3)	11 (61.1)	0.051
Heavy alcohol use (≥50 g/d), *n* (%)	63 (61.2)	48 (69.6)	7 (43.8)	8 (44.4)	**0.045**
Average alcohol duration (mean ± SD), years	28.0 ± 10.6	28.7 ± 10.5	22.3 ± 9.9	29.9 ± 10.4	0.071
Log_{10} HCV viral load (mean ± SD), IU/mL	5.7 ± 0.7	5.8 ± 0.7	5.5 ± 0.9	5.6 ± 0.7	0.17
HCV genotype, *n* (%)					
1	71 (71.3)	50 (73.5)	9 (60.0)	13 (72.2)	0.87
2	16 (15.8)	10 (14.7)	3 (20.0)	3 (16.7)	
3	13 (12.9)	8 (11.8)	3 (20.0)	2 (11.1)	
HCV duration (mean ± SD), years	26.2 ± 1.0	25.7 ± 9.7	21.1 ± 8.4	32.6 ± 9.4	**<0.0010**
Median AST (range), U/L	53 (22–294)	55 (22–331)	46 (26–74)	66.5 (22–155)	0.19
Median ALT (range), U/L	53 (22–294)	69 (19–556)	52 (33–91)	72 (24–208)	0.15
Liver biopsy findings†, *N* (%)					
Inflammation grade ≥ 2	49 (61.3)	33 (63.5)	7 (53.8)	9 (60.0)	0.81
Fibrosis stage ≥2	36 (45.6)	22 (42.3)	5 (38.5)	9 (64.3)	0.29
Steatosis present	28 (35.4)	16 (30.8)	5 (38.5)	7 (50.0)	0.40
HDL (mean ± SD), mg/dL	57.3 ± 14.5	48.3 ± 11.2	62.5 ± 20.4	58.9 ± 14.1	**0.0010**
TG (mean ± SD), mg/dL	101.6 ± 52.8	109 ± 58.3	85.9 ± 39.3	87.4 ± 33.7	0.19

* *P*-values are for overall group comparison and $P < 0.05$ (2-sided) is considered statistically significant.

† Liver biopsy was performed in 80 patients.

Bold values refer to *P*-value<0.05

Table 2

Multivariable analysis of the impact of menopause on insulin resistance (SSPG)

	All patients (*n* = 101)			Patients with liver biopsy (*n* = 78)		
Variables	**Coefficient**	**95% CI**	***P*-value**	**Coefficient**	**95% CI**	***P*-value**
Menopause category (compared to men)			**0.0018**			**0.0002**
Premenopause	48	12, 84	**0.0090**	66	33, 99	**0.0002**
Postmenopause	49	17, 82	**0.0029**	53	16, 90	**0.0053**
Non-white race (compared to white)	50	25, 75	**0.0001**	54	28, 80	**<0.0001**
Waist circumference (per 10 cm)	16.6	6.3, 27	**0.0018**	19.5	8.2, 31	**0.0010**
HDL level (per 10 mg/dL)	−17.8	28, −7.8	**0.0006**	−12.8	24, −1.4	**0.029**
Triglyceride levels, mg/dL	19.2 (per doubling)	0.2, 38	**0.047**	2.7 (per 10 mg/dL)	0.5, 4.8	**0.016**
Liver inflammation grade ≥2 (*vs* <2) on histology				38	10, 66	**0.0094**

Bold values refer to *P*-value<0.05

Table 3

Multivariate analysis of impact of menopause on metabolic syndrome

	All patients (*n* = 103)			Patients with liver biopsy (*n* = 80)		
Variables	**Odds Ratio**	**95% CI**	***P*-value**	**Odds Ratio**	**95% CI**	***P*-value**
Menopause category (compared to men)						
Premenopause	0.51	0.10, 2.6	0.42	0.76	0.12, 4.7	0.76
Postmenopause	1.5	0.4, 5.3	0.52	3.3	0.74, 15.1	0.12
Nonwhite race (compared to white)	6.9	1.5, 32.0	**0.014**	7.8	1.5, 41.7	**0.016**
Liver inflammation grade ≥2 (*vs* <2) on histology				7.9	1.5, 43.2	**0.017**

Bold values refer to *P*-value<0.05