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Original Article

Can gender predict virological response to standard antiviral therapy for chronic hepatitis C? A retrospective study

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ABSTRACT

Aim: The liver is a sexually dimorphic organ presenting gender differences in its metabolism, functions, enzyme activity, membrane lipid composition and immune response. This paper aimed to assess whether gender may predict virological response to standard antiviral therapy in subjects with chronic hepatitis C (CHC). **Methods:** The authors retrospectively analyzed 100 patients with genotype 1 CHC (55 men, 45 women), who performed standard antiviral therapy (interferon and ribavirin for 12 months) in the period 2002-2012, evaluated with blood tests and abdominal ultrasound to compare different virological and biochemical response in both gender. **Results:** Rate of substained virological response (SVR) was higher, but not significant, in women than men (46.7% *vs.* 34.5%, $P = 0.05$); difference became significant after stratification by age (< 50 and ≥ 50 years). Specifically in the group aged under 50 years, rate of SVR was significantly higher in women than in men (66.7% *vs.* 38.2%, $P < 0.05$). **Conclusion:** Female gender may predict virological response to standard antiviral therapy in subjects with CHC aged below 50 years. Considering new potent and more expensive antiviral drugs actually available for HCV treatment, it could be useful to identify candidates firstly eligible to therapy.

Key words: Liver; gender; antiviral therapy

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INTRODUCTION

The liver is a sexually dimorphic organ with gender differences in gene expression, mitochondrial function, microsomal enzyme activity, membrane lipid composition, immunological response. Many studies found gender differences in hepatic response to different stressors, postulating as pattern of secretion and expression of receptors of growth hormones and sex hormone levels may underlie sexual dimorphism. The hepatic circulation depends by a balance between vasoconstrictor and vasodilator substances; in stress conditions, the liver produces prevalent vasodilating substances in females than in males, probably due to estrogens, contributing to protect microcirculation.[1]

Clinical studies also showed how females are more susceptible to the alcohol detrimental effects, as they develop liver disease following alcohol exposure, although reduced in quantity and time. Thus chronic alcohol assumption may modify the

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hormonal balance in both sexes, suggesting a role for sex hormones in the pathogenesis of alcohol-induced liver disease. Furthermore, compared to men, women have a lower volume of distribution and gastric alcohol dehydrogenase activity, so being more prone to liver injury.[2] Furthermore, gender differences have been reported in both incidence and progression of specific liver diseases, such as autoimmune hepatitis, genetic hemochromatosis, non-alcoholic hepatic steatosis and chronic hepatitis C (CHC).

In this study, we aimed to assess whether gender may predict virological response to standard antiviral therapy in subjects with CHC. The identification of predictive factors for response to treatment may allow personalize therapy and improve the cost-effectiveness profile.

METHODS

Patients

We retrospectively evaluated 100 subjects (55 men, 45 women) with genotype 1 CHC who performed standard antiviral therapy [interferon (IFN) and ribavirin for 12 months] in the period 2002-2012, followed by the Department of Medical Science of "San Giovanni Battista" hospital-Turin (Italy). Criteria to start therapy were: serum alanine aminotransferase (ALT) levels 1.2 times the upper limit of the normal range in at least two assessments during the previous 6 months; anti-hepatitis C virus (HCV) antibody positivity; positive polymerase chain reaction for HCV-RNA; hemoglobin values >13 g/dL in males and > 12 g/dL in females, leukocytes count > 3,000 cells/mm^3, platelets (PLTs) count > 100,000 cells/mm^3, normal serum bilirubin, international normalized ratio (INR) and thyroid function tests.

Exclusion criteria included previous antiviral treatments for CHC; co-infections with hepatitis B virus (HBV) or human immunodeficiency virus; immunosuppression state; autoimmune hepatitis; primary biliary cirrhosis; chronic alcohol abuse; uncontrolled psychiatric illness; decompensated cirrhosis; chronic kidney failure; heart disease; hepatocellular carcinoma; pregnancy.

Laboratory analyses and instrumental evaluations

Before treatment, patients underwent routine blood tests [including assessment of complete blood count, aspartate aminotransferase (AST), ALT, gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), total and fractionated bilirubin, alpha-fetoprotein, INR, creatinine, uric acid, cryoglobulins, thyroid hormones, ferritin, HBV serum profile and HCV-RNA], abdominal ultrasound and fibrosis assessment.

Specific anti-HCV antibodies were assessed by chemiluminescence ("chemioluminescent assay", Architect, Abbott Laboratories, AbbottPark, IL).[3,4]

Qualitative and quantitative assessment of HCV RNA were performed using the "COBAS Amplicor HCV system" (sensitivity 50 IU/mL, Roche Molecular Systems, INC., Branchburg, NJ) and the bDNA signal amplification test (sensitivity 615 IU/mL, Branched-DNA version 3.0, Bayer Diagnostics Corporation, Tarritown, NY), respectively, in the period 2002-2007, and the qualiquantitative method COBAS AmpliPrepTM-COBAS TaqManTM (CAP/CTM HCV; sensitivity 15 IU/mL) since 2008.[5-8]

Both HCV RNA genotype and subtype were assessed by reverse hybridization line probe assay (INNO-LIPA, Innogenetics, Ghent, Belgium).[9]

Hepatic steatosis, assessed by ultrasound, was defined as an increased liver parenchyma echogenicity compared to the spleen or to the right kidney, the attenuation of the ultrasound beam in depth tissues and the loss of echoes in the portal veins walls according to the following grade scoring system: grade 0, normal echogenicity, absence of differences between echogenicity of liver and kidney; grade 1, mild steatosis with increased echogenicity of liver compared to kidney, absence of attenuation of the ultrasound beam, possibility to explore the depth of hepatic parenchyma; grade 2, moderate increase of steatosis with higher echogenicity of the liver, attenuation of ultrasound beam in depth, loss of echoes from the peripheral portal branches; and grade 3, advanced steatosis with marked increase in echogenicity, attenuation of ultrasound beam in depth and loss of echoes from the major portal branches.

Fibrosis was assessed by elastography (FibroScan elastography) and defined as follows: F0 (up to 5 KPa), F1 (5 to 8.9 KPa), F2 (8.9 to 11 KPa), F3 (11 to 14.5 KPa), F4 (> 14.5 KPa).[10]

In subjects not underwent to FibroScan (n = 33, males = 18), fibrosis was estimated by the FIB-4 method, according to the formula: [age (years) × AST (U/L)] / PLTs (10^9/L) × [ALT (U/L)]$^{1/2}$ and defined

according to the score: < 1.45 was considered as FO-F1; 1.45-3.25 was considered as F2; > 3.25 was considered as F3-F4.

Treatment

Standard treatment consisted in pegylated IFN alfa-2a 180 μg s.c. once a week or pegylated IFN alfa-2b 1-1.5 μg/kg s.c. once a week plus ribavirin (800 mg/day for patients weighing < 70 kg, 1,000 mg/day for patients weighing 70-80 kg, 1,200 mg/day for patients weighing > 80 kg) for 48 weeks.

In the presence of adverse events, both IFN and ribavirin doses were reduced by 25% and down to 200 mg, respectively; both were stopped when hemoglobin < 8.5 g/dL and/or leukocytes count < 2,000 cells/mm^3 and/or PLTs count < 50,000/mm^3.

Treatment efficacy was assessed according to rapid virological response (RVR, undetectable HCV RNA at week 4 of treatment); early virological response (EVR), including complete EVR (cEVR, undetectable HCV RNA at week 12 of treatment in the absence of RVR) and partial EVR (pEVR, ≥ 2 log reduction of serum HCV RNA at week 12 of therapy compared with the baseline level, in the absence of RVR or cEVR); end-of-treatment virologic response (ETVR, undetectable HCV RNA at the end of treatment); sustained virological response (SVR, HCV RNA negativity at the end of treatment and in the after 24 weeks); relapse was defined as undetectable HCV RNA at end of treatment and detectable HCV RNA during follow-up.

Subjects were followed monthly, until the end of therapy. Thereafter, subjects showing ETVR were observed during the following 24 weeks, in order to verify either the persistence SVR or the loss of response.

Statistical analysis

Data were expressed as means ± SD (continuous variables) or proportions (categorical values). *T*-test and Chi-square test were used to evaluate group differences in means and proportions, respectively. Univariate analysis was performed on baseline parameters to identify factors potentially related to SVR. All *P* values were two sided, considering statistically significant a *P* value < 0.05. All analyses were performed with Statistical Package for the Social Science version 20.0.

RESULTS

Assessment of baseline characteristics

Baseline characteristics, laboratory data and the degree of steatosis and fibrosis are summarized in Tables 1-6. Baseline characteristics, laboratory data and the degree of both steatosis and fibrosis were comparable in men and women, excepted for haemoglobin, GGT and uric acid values, resulted significantly higher in men. Similar results were obtained after stratification of participants by gender and age < or > 50 years; haemoglobin and GGT values were significantly higher in men compared to women both aged less and more than 50 years. Cryoglobulins positivity occurred more frequently in women aged more than 50 years ($P = 0.05$).

Table 1: Comparison of baseline serum chemistry parameters between males and females in the whole sample

	Whole sample (*n* = 100)		Student's *T*-test	*P* value
	Male (*n* = 55)	Female (*n* = 45)		
Age (years)	45.6 ± 11	48.8 ± 11.6	-1.43	0.156
PLTs (× 10^9/L)	202 ± 46	220 ± 69	-1.534	0.128
Hb (g/dL)	15.2 ± 1.38	13.78 ± 1.36	4.774	0
WBC (× 10^9/L)	6 ± 1.6	5.5 ± 1.5	1.318	0.191
AST (U/L)	56 ± 46	56 ± 44	0.03	0.976
ALT (U/L)	95 ± 72	72 ± 64	1.653	0.102
GGT (U/L)	96 ± 87	42 ± 31	4.568	0
ALP (U/L)	89 ± 36	98 ± 48	-0.327	0.746
Total bilirubin (mg/dL)	0.96 ± 0.43	0.79 ± 0.26	1.878	0.065
INR	1.1 ± 0.3	1 ± 0.1	1.954	0.059
Uric acid (mg/dL)	5.6 ± 1.3	4.3 ± 1	3.854	0
AFP (ng/mL)	9.3 ± 9.9	6.7 ± 4.8	1.026	0.312
HCV RNA (log_{10} UI/mL)	5.7 ± 0.64	5.8 ± 0.64	-0.445	0.657
Cryoglobulins (+/-)	3/52	6/39	Chi = 1.88	0.17
Ferritin (ng/mL)	308 ± 469	134 ± 115	1.624	0.111

Data are shown as mean ± SD. PLT: platelet; Hb: hemoglobin; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyltransferase; ALP: alkaline phosphatase; INR: international normalized ratio; AFP: alpha-fetoprotein; HCV: hepatitis C virus

Table 2: Comparison of baseline serum chemistry parameters between males and females respectively in the < 50 and > 50 year-aged patient samples

	< 50 years sample (*n* = 55)				> 50 years sample (*n* = 45)			
	Male (*n* = 34)	Female (*n* = 21)	Student's *T*-test	*P* value	Male (*n* = 21)	Female (*n* = 24)	Student's *T*-test	*P* value
Age (years)	38.2 ± 5.7	38.1 ± 7.1	0.053	0.958	57.5 ± 5.6	58.2 ± 4.1	-0.467	0.643
PLTs (× 10^9/L)	212 ± 38	235 ± 55	-1.235	0.222	187 ± 54	206 ± 78	-0.901	0.373
Hb (g/dL)	15.5 ± 1.37	13.8 ± 1.1	4.371	0	15 ± 1	13.74 ± 1.58	3.021	0.005
WBC (× 10^9/L)	6 ± 1.5	6 ± 1.48	0.077	0.939	5.8 ± 1.74	5.1 ± 1.3	1.409	0.168
AST (U/L)	55 ± 54	43 ± 35	0.877	0.384	56 ± 27	66 ± 49	-0.879	0.384
ALT (U/L)	98 ± 82	62 ± 52	1.769	0.083	89 ± 48	80 ± 73	0.474	0.638
GGT (U/L)	105 ± 91	27 ± 20	4.583	0	75 ± 75	54 ± 34	1.194	0.239
ALP(U/L)	85 ± 42	97 ± 52	-0.361	0.724	94 ± 28	100 ± 45	-0.303	0.766
Total bilirubin (mg/dL)	0.94 ± 0.47	0.77 ± 0.25	1.294	0.203	1 ± 0.3	0.8 ± 0.2	1.659	0.108
INR	1.1 ± 0.3	1 ± 0.0	1.053	0.301	1.1 ± 0.2	1 ± 0.1	1.503	0.16
Uric acid (mg/dL)	5.6 ± 1.3	4.6 ± 0.7	1.032	0.314	5.6 ± 1.2	4.61 ± 1.1	3.036	0.006
AFP (ng/mL)	5.2 ± 2.9	4.1 ± 3.2	0.694	0.498	1.4.5 ± 13.2	8.3 ± 5	1.194	0.272
HCV RNA ($\log_{10}$ UI/mL)	5.66 ± 0.71	5.63 ± 0.75	0.094	0.926	5.86 ± 0.52	5.98 ± 0.48	-0.737	0.466
Cryoglobulins (+/-)	3/31	2/19	Chi = 0.008	0.93	0/21	4/20	Chi = 3.84	0.05
Ferritin (ng/mL)	307 ± 77	26 ± 60	1.363	0.183	310 ± 191	357 ± 130	0.997	0.331

Data are shown as mean ± SD. PLT: platelet; Hb: hemoglobin; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyltransferase; ALP: alkaline phosphatase; INR: international normalized ratio; AFP: alpha-fetoprotein; HCV: hepatitis C virus

Table 3: Degree of fibrosis and steatosis in the whole sample considering males and females, value of the Chi-square test and the related *P* value

	Whole sample (*n* = 100)		Chi-square test	*P* value
	Male (*n* = 55)	Female (*n* = 45)		
Fibrosis, *n* (%)			0.069	0.966
0-1	34 (61.8%)	28 (62%)		
2	12 (21.8%)	9 (20%)		
3-4	9 (16.4%)	8 (18%)		
Steatosis, *n* (%)*			0.488	0.921
Assessment	19 (35.85%)	13 (31%)		
Light	13 (24.5%)	12 (28.6%)		
Mild	19 (35.85%)	16 (38%)		
Advanced	2 (3.8%)	1 (2.4%)		

*Steatosis degree has been assessed only in 95 subjects (53 males and 42 females), resulting 5 ultrasonographic investigations poorly reliable

Table 4: Degree of fibrosis and steatosis considering males and females, value of the Chi-square test and the related *P* value respectively in the < 50 and > 50 year-aged patient samples

	< 50 years sample (*n* = 55)				> 50 year sample (*n* = 45)			
	Male (*n* = 34)	Female (*n* = 21)	Chi-square test	*P* value	Male (*n* = 21)	Female (*n* = 24)	Chi-square test	*P* value
Fibrosis, *n* (%)			4.954	0.0839			0.145	0.929
0-1	27 (79.4%)	21 (100%)			7 (33.3%)	7 (29.2%)		
2	4 (11.8%)	0 (0%)			8 (38.1%)	9 (37.5%)		
3-4	3 (8.8%)	0 (0%)			6 (28.6%)	8 (33.3%)		
Steatosis, *n* (%)*			1.8127	0.612			3.1	0.375
Assessment	11 (33.3%)	9 (45%)			8 (40%)	4 (18.2%)		
Light	8 (24.2%)	5 (25%)			5 (25%)	7 (31.8%)		
Mild	12 (36.4%)	6 (30%)			7 (35%)	10 (45.5%)		
Advanced	2 (6.1)	0 (0%)			0 (0%)	1 (4.5%)		

*Steatosis degree has been assessed only in 95 subjects (33 males < 50 years, 20 females < 50 years, 20 males > 50 years, and 22 females > 50 years), resulting 5 ultrasonographic investigations poorly reliable

Assessment of virological response

Forty patients reached a SVR (SVR rate 40%); and 60 patients were negative at the end of the treatment (ETVR rate 60%), but among these 20 fell in the later 24 weeks, with a 33.3% relapse rate.

In the whole sample < 50 years patients showed a significant rate of SVR ($P = 0.040$) [Table 6], due to < 50 years women who achieved significant higher rates of both ETVR ($P = 0.001$) and SVR ($P = 0.01$) compared to males of similar age [Table 7, Figures 1

Table 5: Comparison of virologic response rates between males and females in the whole sample

	Whole sample (*n* = 100)		Chi-square test	*P* value
	Male (*n* = 55)	Female (*n* = 45)		
RVR	5/55 (9.1%)	6/45 (13.3%)	0.455	0.5
cEVR	13/55 (23.6%)	16/45 (35.6%)	1.708	0.191
pEVR	16/55 (29.1%)	13/45 (28.9%)	0	0.982
Absence of RVR or cEVR or pEVR	21/55 (38.2%)	10/45 (22.2%)	2.947	0.086
ETVR	30/55 (54.5%)	30/45 (66.7%)	1.515	0.218
Relapse rate	11/30 (36.7%)	9/30 (30%)	0.30	0.584
SVR	19/55 (34.5%)	21/45 (46.7%)	1.515	0.218

Data are shown as *n/N* (%). RVR: rapid virological response; EVR: early virological response; cEVR: complete EVR; pEVR: partial EVR; ETVR: end-of-treatment virologic response; SVR: sustained virological response

Table 6: Comparison of virologic response rates between males and females respectively in the < 50 and > 50 year-aged patient samples

	< 50 year sample (*n* = 55)				> 50 year sample (*n* = 45)			
	Male (*n* = 34)	Female (*n* = 21)	Chi-square test	*P* value	Male (*n* = 21)	Female (*n* = 24)	Chi-square test	*P* value
RVR	4/34 (11.8%)	5/21 (23.8%)	1.376	0.241	1/21 (4.8%)	1/24 (4.2%)	0.009	0.923
CEVR	11/34 (32.4%)	12/21 (57.1%)	3.279	0.070	2/21 (9.5%)	4/24 (16.7%)	0.494	0.48
PEVR	4/34 (11.8%)	2/21 (9.5%)	0.067	0.796	12/21 (57.1%)	11/24 (45.8%)	0.573	0.44
Absence of RVR or cEVR or pEVR	15/34 (44.1%)	2/21 (9.5%)	7.275	0.007	6/21 (28.6%)	8/24 (33.3%)	0.118	0.73
ETVR	19/34 (55.9%)	19/21 (90.5%)	7.275	0.007	11/21 (52.4%)	11/24 (45.8%)	0.192	0.66
Relapse rate	6/19 (31.6%)	5/19 (26.3%)	0.128	0.7206	5/11 (45.5%)	4/11 (36.4%)	0.188	0.66
SVR	13/34 (38.2%)	14/21 (66.7%)	4.199	0.04	6/21 (28.6%)	7/24 (29.2%)	0	0.964

Data are shown as *n/N* (%). RVR: rapid virological response; EVR: early virological response; cEVR: complete EVR; pEVR: partial EVR; ETVR: end-of-treatment virologic response; SVR: sustained virological response

Table 7: Comparison of virologic response rates between < 50 year-aged and > 50 year-aged male sample and between < 50 year-aged and > 50 year-aged female sample

	Male sample (*n* = 55)				Female sample (*n* = 45)			
	< 50 years (*n* = 34)	> 50 years (*n* = 21)	Chi-square test	*P* value	< 50 years (*n* = 21)	> 50 years (*n* = 24)	Chi-square test	*P* value
RVR	4/34 (11.8%)	1/21 (4.8%)	0.77	0.38	5/21 (23.8%)	1/24 (4.2%)	3.73	0.0531
cEVR	11/34 (32.4%)	2/21 (9.5%)	3.74	0.053	12/21 (57.1%)	4/24 (16.7%)	8	0.004
pEVR	4/34 (11.8%)	12/21 (57.1%)	12.95	0.0003	2/21 (9.5%)	11/24 (45.8%)	7.187	0.007
Absence of RVR or cEVR or pEVR	15/34 (44.1%)	6/21 (28.6%)	1.329	0.24	2/21 (9.5%)	8/24 (33.3%)	3.67	0.0553
ETVR	19/34 (55.9%)	11/21 (52.4%)	0.064	0.8	19/21 (90.5%)	11/24 (45.8%)	10.04	0.001
Relapse rate	6/19 (31.6%)	5/11 (45.5%)	0.577	0.44	5/19 (26.3%)	4/11 (36.4%)	0.33	0.56
SVR	13/34 (38.2%)	6/21 (28.6%)	0.536	0.464	14/21 (66.7%)	7/24 (29.2%)	6.32	0.01

Data are shown as *n/N* (%). RVR: rapid virological response; EVR: early virological response; cEVR: complete EVR; pEVR: partial EVR; ETVR: end-of-treatment virologic response; SVR: sustained virological response

and 2]. On the other hand, frequency of subjects not achieving RVR or EVR was significantly higher in men > 50 years than in females [Table 7]. No significant differences existed in virological responses in subjects > 50 years.

Influence of age among patients of the same gender

Analysis performed in subjects of the same gender stratified by age showed significantly higher rates of pEVR in males > 50 years compared to < 50 years males. Furthermore, women < 50 years were characterised by significantly higher rates of cEVR, ETVR, SVR and by significantly lower rates of pEVR compared to women > 50 years [Figure 3].

Univariate analysis

In univariate analysis, factors associated with SVR were presence of RVR, a lower level of GGT, a degree

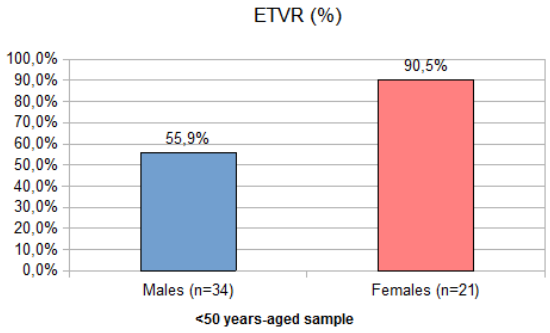

Figure 1: End-of treatment virological response (ETVR) in the < 50 year-aged sample

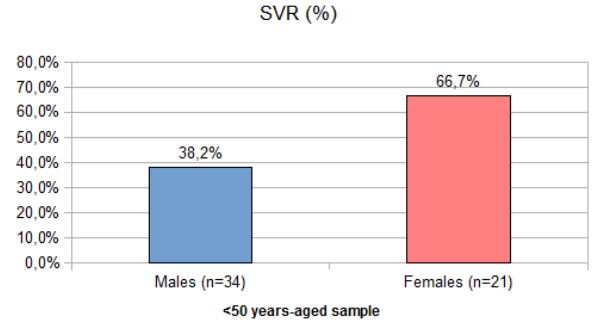

Figure 2: Sustained virological response (SVR) in the < 50 year-aged sample

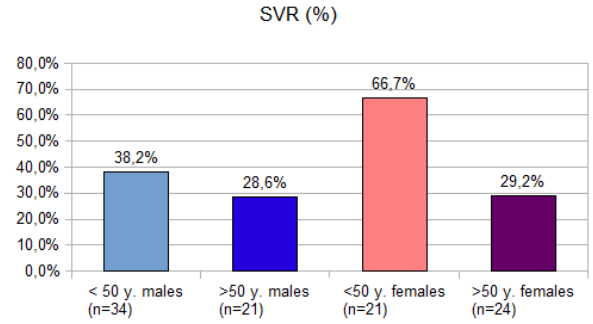

Figure 3: Sustained virological response (SVR) in < 50 year-aged and > 50 year-aged male and female sample

of fibrosis F0-2. Both age and female gender were associated with SVR within the subgroup of subjects < 50 years [Figure 3].

DISCUSSION

Our survey has compared men and women before considering the overall sample and afterwards analyzing separately a group of patients younger than 50 years with a group of patients older than 50 years.

This study considered biochemical and ultrasonographical characteristics, presence of fibrosis at baseline, several types of virological response.

Few meaningful differences in biochemical characteristics between genders have been found. Haemoglobin was significantly lower in women compared with men either in < 50 or in > 50 years patients; the uric acid was significantly higher in men either in the whole sample and in the > 50 years group; GGT-set was significantly higher in men in the overall sample and in the < 50 years group.

In women with menopause, hepatic steatosis was more frequent and severe than in men:[11] menopause may correlate with necro-inflammation, steatosis and metabolic alterations (high levels of cholesterol and glycemia). Steatosis showed a higher prevalence in chronic-HCV patients in post-menopause (> 55 years); moreover the pro-inflammation state related with menopause may cause a moderate to severe fibrosis progression, leading to an inefficient response to antiviral therapy.[12,13]

In our sample, the pre-treatment steatosis level did not differ meaningfully in two genders either in the whole sample or in younger and older than 50 years groups. The presence of fibrosis at baseline was not associated to gender either in the overall sample or in two examinated groups.

Studies on natural history and predictors of severity disease showed that the evolution of sickness presented a high inter-individual variability and several factors were associated to progression in fibrosis.

Rigamonti *et al.*[14] stressed as the gender may influence the progression of CHC only in young patients: in < 50 years women emerged lower necro-inflammation and fibrosis than in same aged men, whilst in > 50 years women and men authors did not noticed differences in the disease severity.

In literature effects of gender remain a controversial topic not only as regards the therapy outcome but also relatively to the spontaneous clearance of infection, to the developments of infection linked complications, to the outcomes after liver transplantation.[13,15]

Several studies demonstrate a higher clearance in women than in men; steroid hormones would play a role for the gender-specific susceptibility of infection even though any sufficiently exhaustive model has not been submitted yet.[16]

In order to identify factors able to predict SVR, our univariate analysis considered biochemical

and ultrasonographical parameters, and presence of fibrosis at baseline: beyond age and gender, the factors appeared associated to SVR were RVR, GGT levels and 0-2 fibrosis. RVR was a powerful predictive factor of SVR in previous studies, showing as patients with RVR had ratio of SVR meaningfully higher than others; moreover some studies suggest RVR as the most important SVR predictor.[17-20]

Villela-Nogueira *et al*.[21] identified that higher levels of GT during a pre-treatment may be a independent negative predictive factor of response to treatment: being a biochemical parameter easily available and at low cost, it may be incorporated in evaluation of response to treatment alongside with other predictive factors.

In conclusion several studies demonstrated that higher degrees of fibrosis have been associated with lower rates of response. To evaluate the effectiveness of treatment, several indicators of response were analysed, in particular SVR which represents the optimal outcome of treatment. There is no concordance of opinion concerning the gender role on the response to the treatment.

In literature there are few studies which identify alike responses in two genders after making comparisons between men and women in patients younger than 40-50 years. Two recent works do not detect a significant influence of genre even though both identified a meaningfully greater response in women younger than 40-50 years compared to the eldest ones Other studies consider the male gender as one of the strongest factors to predict SVR.[17,25] Furthermore data concerning rates of SVR in women are conflicting; studies which identified female gender as an independent factor linked to SVR or which noticed as not exist meaningful differences in genders were not stratified by age and considered not differences in female hormonal status;[20,22,23] other studies suggested a better response in women even after splitting the sample into age groups.[13,19,23,24]

Few studies lead to identify alike responses in < 40-50 year-old patients of both genders: recent works detected not a significant influence of gender even though in presence of a better response in < 40-50 year-old women compared to the elder ones; other studies considered the male gender as a strong factors to predict SVR.

Our outcomes did not identify meaningful association between virological responses and gender considering the whole sample: RVR, cEVR, ETVR and SVR frequencies were higher in woman and the relapse rate was higher in men even though no statistically significant difference resulted, so indicating as the gender influences not the therapy outcome.

Nevertheless meaningful gender differences emerged after stratification by age (< and > 50 years). We noticed < 50 years aged women had a higher frequency of response and a lower relapse rate compared to men belonging to the same age group, differences appearing statistically meaningful due to the absence of RVR, cEVR, ETVR, and SVR, suggesting as female gender would be a positive predictive factor of response to the therapy.

Otherwise, in the > 50 years aged group frequency of RVR and ETVR appeared higher in men whilst SVR was slightly higher in women: men had higher relapse ratio compared to women and so reaching less frequently SVR. The evidence of a better response to therapy in < 50 year-old females than in co-aged men and of an alike response in the > 50 years in both groups leads to formulate several hypotheses. It may be supposed only a worsening in women older than 50 years compared to those younger ones linked to an alike response among men before and after 50 years, or we may assume a deterioration with age in both genders even though it is more accentuated in women. Another theory considered the possibility of a rapprochement between sexes with age linked to a worsening in female gender and an improvement in > 50 year-old males. Finally, it could exist an improvement in men with age up to the level of women younger than 50 years without a real worsening of women older than 50 years; this condition may be true whether there is a meaningful improvement in men older than 50 years and an alike response in > 50 year-old women compared with younger and same gender patients.

Comparing the response frequencies in younger and older than 50 year-old males, we could exclude the last two hypothesis, having observed a less response in > 50 year-old patients in both genders without an improvement in these men compared to the < 50 year-old ones.

Since women responded to the treatment differently by age and they achieved the viral clearance more frequently than men, the hormonal activity and especially oestrogen levels may be associated to

SVR;[11,26] many metabolic processes may be involved, related to the reduction in the oestrogen serum concentration after menopause,[27] although it has been not separately considered in our study; many data from literature suggested as the reproductive state may be an important factor in predicting the response to antiviral therapy.[26] These observations suggest as women in reproductive age with CHC should be treated even if liver disease is moderate, being this condition linked to oestrogens exposure.[28]

Results obtained from our comparison between younger and elder women and younger and elder men showed in the group of women a meaningful worsening in > 50 year-old patients compared to younger ones whilst this difference was not so significant in the group of men although there was a worse response after 50 years. This suggested the lost of the advantage in female gender after 50 years without having a worsening in both genders with age.

In summary, even if affected by limitations related to retrospective and in subgroups analysis, the outcomes we obtained reveal not meaningful differences between men and women when the whole sample is examined without stratification by age whilst an influence of gender on the response to the treatment is identified when patients were divided in two groups younger or elder than 50 years. Despite the grade of influence of gender on standard treatment is still debated, we noticed as the female gender may be considered a positive predictor of response to therapy, taking into account its strong interaction with age and inserting in a broader context made of several modifiable and non-modifiable predictive factors related to the host and virus. Considering both high efficacy and costs of new antiviral drugs therapy protocols, the evidence of a gender- and age- different response to the standard treatment may play a role in changing epidemiologic characteristics of eligible patients and asks the question if certain groups of patients should be primarily treated.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Yokoyama Y, Nimura Y, Nagino M, Bland KI, Chaudry IH. Current understanding of gender dimorphism in hepatic pathophysiology. *J Surg Res* 2005;128:147-56.
2. Shimizu I, Kohno N, Tamaki K, Shono M, Huang HW, He JH, Yao DF. Female hepatology: favorable role of estrogen in chronic liver disease with hepatitis B virus infection. *World J Gastroenterol* 2007;13:4295-305.
3. Ismail N, Fish GE, Smith MB. Laboratory evaluation of a fully automated chemiluminescence immunoassay for rapid detection of HBsAg, antibodies to HBsAg, and antibodies to hepatitis C virus. *J Clin Microbiol* 2004;42:610-7.
4. Jonas G, Pelzer C, Beckert C, Hausmann M, Kapprell HP. Performance characteristics of the ARCHITECT anti-HCV assay. *J Clin Virol Off Publ Pan Am Soc Clin Virol* 2005;34:97-103.
5. Krajden M, Ziermann R, Khan A, Mak A, Leung K, Hendricks D, et al. Qualitative detection of hepatitis C virus RNA: comparison of analytical sensitivity, clinical performance, and workflow of the Cobas Amplicor HCV test version 2.0 and the HCV RNA transcription-mediated amplification qualitative assay. *J Clin Microbiol* 2002;40:2903-7.
6. Pittaluga F, Allice T, Abate ML, Ciancio A, Cerutti F, Varetto S, Colucci G, Smedile A, Ghisetti V. Clinical evaluation of the COBAS Ampliprep/COBAS TaqMan for HCV RNA quantitation in comparison with the branched-DNA assay. *J Med Virol* 2008;80:254-60.
7. Elbeik T, Surtihadi J, Destree M, Gorlin J, Holodniy M, Jortani SA, Kuramoto K, Ng V, Valdes R Jr, Valsamakis A, Terrault NA. Multicenter evaluation of the performance characteristics of the bayer VERSANT HCV RNA 3.0 assay (bDNA). *J Clin Microbiol* 2004;42:563-9.
8. Sizmann D, Boeck C, Boelter J, Fischer D, Miethke M, Nicolaus S, Zadak M, Babiel R. Fully automated quantification of hepatitis C virus (HCV) RNA in human plasma and human serum by the COBAS AmpliPrep/COBAS TaqMan system. *J Clin Virol* 2007;38:326-33.
9. Nolte FS, Green AM, Fiebelkorn KR, Caliendo AM, Sturchio C, Grunwald A, Healy M. Clinical evaluation of two methods for genotyping hepatitis C virus based on analysis of the 5' noncoding region. *J Clin Microbiol* 2003;41:1558-64.
10. Armstrong MJ, Corbett C, Hodson J, Marwah N, Parker R, Houlihan DD, Rowe IA, Hazlehurst JM, Brown R, Hübscher SG, Mutimer D. Operator training requirements and diagnostic accuracy of Fibroscan in routine clinical practice. *Postgrad Med J* 2013; 89:685-92.
11. Codes L, Asselah T, Cazals-Hatem D, Tubach F, Vidaud D, Paraná R, Bedossa P, Valla D, Marcellin P. Liver fibrosis in women with chronic hepatitis C: evidence for the negative role of the menopause and steatosis and the potential benefit of hormone replacement therapy. *Gut* 2007;56:390-5.
12. Fierbinţeanu-Braticevici C, Mohora M, Tribus L, Petrişor A, Creţoiu SM, Creţoiu D, Usvat R, Ioniţă L. Hepatocyte steatosis in patients infected with genotype 1 hepatitis C virus. *Romanian J Morphol Embryol* 2010;51:235-42.
13. Villa E, Karampatou A, Cammà C, Di Leo A, Luongo M, Ferrari A, Petta S, Losi L, Taliani G, Trande P, Lei B, Graziosi A, Bernabucci V, Critelli R, Pazienza P, Rendina M, Antonelli A, Francavilla A. Early menopause is associated with lack of response to antiviral therapy in women with chronic hepatitis C. *Gastroenterology* 2011;140:818-29.
14. Rigamonti C, Andorno S, Maduli E, Capelli F, Boldorini R, Sartori M. Gender and liver fibrosis in chronichepatitis: the role of iron status. *Aliment Pharmacol Ther* 2005;21:1445-51.
15. Lao XQ, Thompson A, McHutchison JG, McCarthy JJ. Sex and age differences in lipid response to chronic infection with the hepatitis C virus in the United States National Health and Nutrition Examination Surveys. *J Viral Hepat* 2011;18:571-9.
16. Bakr I, Rekacewicz C, El Hosseiny M, Ismail S, El Daly M, El-Kafrawy S, Esmat G, Hamid MA, Mohamed MK, Fontanet A. Higher clearance of hepatitis C virus infection in females compared with males. *Gut* 2006;55:1183-7.
17. Aziz H, Gil ML, Waheed Y, Adeeb U, Raza A, Bilal I, Athar MA. Evaluation of prognostic factors for Peg Interferon alfa-2b plus ribavirin treatment on HCV infected patients in Pakistan. *Infect Genet Evol* 2011;11:640-5.
18. Idrees M, Riazuddin S. A study of best positive predictors for

sustained virologic response to interferon alpha plus ribavirin therapy in naive chronic hepatitis C patients. *BMC Gastroenterol* 2009;9:5.
19. Yu JW, Sun LJ, Zhao YH, Kang P, Yan BZ. Impact of sex on virologic response rates in genotype 1 chronic hepatitis C patients with peginterferon alpha-2a and ribavirin treatment. *Int J Infect Dis* 2011;15:e740-6.
20. Akram M, Idrees M, Zafar S, Hussain A, Butt S, Afzal S, Rehman IU, Liaqat A, Saleem S, Ali M, Butt A. Effects of host and virus related factors on interferon-α+ribavirin and pegylated-interferon+ribavirin treatment outcomes in chronic Hepatitis C patients. *Virol J* 2011;8:234.
21. Villela-Nogueira CA, Perez RM, de SegadasSoares JA, Coelho HSM. Gamma-glutamyltransferase (GGT) as an independent predictive factor of sustained virologic response in patients with hepatitis C treated with interferon-alpha and ribavirin. *J Clin Gastroenterol* 2005;39:728-30.
22. Hu CC, Lin CL, Kuo YL, Chien CH, Chen SW, Yen CL, Lin CY, Chien RN. Efficacy and safety of ribavirin plus pegylated interferon alfa in geriatric patients with chronic hepatitis C. *Aliment Pharmacol Ther* 2013;37:81-90.
23. Innes HA, Hutchinson SJ, Allen S, Bhattacharyya D, Bramley P, Carman B, Delahooke TE, Dillon JF, Goldberg DJ, Kennedy N, Mills PR, Morris J, Morris J, Robertson C, Stanley AJ, Hayes P; Hepatitis C Clinical Database Monitoring Committee. Ranking predictors of a sustained viral response for patients with chronic hepatitis C treated with pegylated interferon and ribavirin in Scotland. *Eur J Gastroenterol Hepatol* 2012;24:646-55.
24. Floreani A, Cazzagon N, Boemo DG, Baldovin T, Baldo V, Egoue J, Antoniazzi S, Minola E. Female patients in fertile age with chronic hepatitis C, easy genotype, and persistently normal transaminases have a 100% chance to reach a sustained virological response. *Eur J Gastroenterol Hepatol* 2011;23:997-1003.
25. Aziz H, Athar MA, Murtaza S, Irfan J, Waheed Y, Bilal I, Raza A. Predictors of response to antiviral therapy in patients with chronic hepatitis C from Pakistani population. *Chin Med J (Engl)* 2011;124:1333-7.
26. Hayashi J, Kishihara Y, Ueno K, Yamaji K, Kawakami Y, Furusyo N, Sawayama Y, Kashiwagi S. Age-related response to interferon alfa treatment in women *vs* men with chronic hepatitis C virus infection. *Arch Intern Med* 1998;158:177-81.
27. Sezaki H, Suzuki F, Kawamura Y, Yatsuji H, Hosaka T, Akuta N, Kobayashi M, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Miyakawa Y, Kumada H. Poor response to pegylated interferon and ribavirin in older women infected with hepatitis C virus of genotype 1b in high viral loads. *Dig Dis Sci* 2009;54:1317-24.
28. Villa E, Cammà C, Di Leo A, Karampatou A, Enea M, Gitto S, Bernabucci V, Losi L, De Maria N, Lei B, Ferrari A, Vukotic R, Vignoli P, Rendina M, Francavilla A. Peginterferon-A_2B plus ribavirin is more effective than peginterferon-A_2A plus ribavirin in menopausal women with chronic hepatitis C. *J Viral Hepat* 2012;19:640-9.