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# Impact of sex on virologic response rates in genotype 1 chronic hepatitis C patients with peginterferon alpha-2a and ribavirin treatment

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SUMMARY

*Objectives:* The relationship between patient sex and the effectiveness of peginterferon alpha-2a and ribavirin treatment in chronic hepatitis C (CHC) patients remains unclear. The aim of this study was to investigate the impact of sex on virologic responses rates in genotype 1 CHC patients.

*Methods:* A matched retrospective cohort study of 630 genotype 1 patients treated with peginterferon and ribavirin derived from our hospital database was conducted. These patients were divided into three groups according to age: patients aged <40 years ($n$ = 200), patients aged 40–50 years ($n$ = 210), and patients aged 51–60 years ($n$ = 220). The rate of patients receiving ≥80% of the planned drug dose and virologic response rates were compared between males and females in the three groups. Factors influencing the sustained virologic response (SVR) were studied by multivariate analysis.

*Results:* In patients aged 51–60 years, the rate of female patients receiving ≥80% of the planned ribavirin dose was significantly lower than that of males (42.7%, 47/110 vs. 61.8%, 68/110; Chi-square = 8.035, $p$ = 0.005). In patients aged <40 years, the SVR rate of females was significantly higher than that of males (75%, 75/100 vs. 54%, 54/100; Chi-square = 9.630, $p$ = 0.002); in patients aged 40–50 years, there was no significant difference in the SVR rate between males and females (50.5%, 53/105 vs. 54.3%, 57/105; Chi-square = 0.305, $p$ = 0.580); in patients aged 51–60 years, the SVR rate of females was significantly lower than that of males (33.6%, 37/110 vs. 48.2%, 53/110; Chi-square = 4.814, $p$ = 0.028). In multivariate logistic regression analysis, the independent factors associated with SVR in patients aged 51–60 years were sex ($p$ = 0.013), ≥80% of the planned ribavirin dose ($p$ = 0.008), and the presence of a rapid virologic response ($p$ = 0.001).

*Conclusions:* In the group of patients aged <40 years, the SVR rate of females was higher than that of males; in the group of patients aged 40–50 years, females and males shared similar SVR rates; in the group of patients aged 51–60 years, the SVR rate of females was lower than that of males.



## 1. Introduction

Chronic hepatitis C (CHC) is a serious global health concern. Despite a similar prevalence, the rates of progression of fibrosis in CHC differ significantly between males and females. Clinical observations show that chronic liver disease progresses more rapidly to cirrhosis in males than females.[1] The severity of fibrosis in CHC is also significantly different between males and females.[2] Recent data strongly suggest that estrogens and/or estrogen receptors have an impact on the course of liver disease. A number of studies suggest that the estrogen, at physiological levels, presents an antifibrogenic action probably through an antioxidant effect, decreasing the levels of lipid peroxidation products in the liver and blood, thus inhibiting the myofibroblastic transformation of stellate cells and contributing to gender-associated differences in relation to the development of fibrosis.[3] A decrease in estrogen receptors, marked after the menopause, is reported to be associated with increased lipid peroxidation and impaired superoxide dismutase function, leading to increased susceptibility to hepatic fibrosis or hepatocellular carcinoma (HCC).[4] There is evidence for a potentially favorable effect on hepatic fibrosis in relation to the use of hormone replacement therapy (HRT) in women with CHC after the menopause.[5] On the other hand, women are less tolerant to ribavirin owing to hemolytic side-effects.[6] In older female patients, lower average cumulative exposure to ribavirin results in high relapse rates and low sustained virologic response (SVR) rates.[7] Therefore, older female patients may have negative prognostic factors for SVR, such as advanced fibrosis or lower cumulative exposure to ribavirin.

Combination therapy with pegylated interferon (PEG-IFN) and ribavirin is the current first-line therapy used to eliminate hepatitis C virus (HCV) in patients with CHC.[8] Independent

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prognostic factors for SVR include viral genotype non-1, low pretreatment viral load, the absence of cirrhosis or fibrosis, and female gender.[9] Age and sex may affect the efficacy of antiviral therapy. People aged over 40 years are progressively more susceptible to faster rates of fibrosis. The SVR rate is low in patients with advanced liver fibrosis. Data from a meta-analysis and large, randomized, clinical trials of combination therapy with PEG-IFNα plus ribavirin have shown that age older than 40 years is an independent predictor of a reduced SVR.[10] The influence of gender on treatment with PEG-IFN and ribavirin is still under debate. In a previous study, the response to IFN treatment was shown to be better in women than in men.[11] Sezaki and colleagues[12] have reported that response to combined PEG-IFN and ribavirin is poorer in female than male patients with hepatitis C who are aged >50 years, and that the low tolerance to ribavirin and low estrogen levels in older women could be responsible for their impaired response. Narciso-Schiavon et al. proved that the rate of SVR did not differ between the genders.[13] Kainuma et al.[14] found no significant differences between the sexes, and their data suggest that age may be a more important factor than sex for increasing the rate of SVR.

There remains a possibility that the SVR rate could be influenced by age. Hence, there is the need for a comparison of the response between men and women in different age groups. To collect more convincing evidence of different therapeutic effects between male and female patients, we utilized a well-designed matched retrospective cohort study to control the bias of patient selection.

## 2. Methods

### 2.1. Study population and study design

CHC patients were diagnosed by the presence of serum antibodies to HCV, detectable serum HCV RNA, and compensated liver disease. Patients were excluded if they had hepatitis A or B or D or E, or HIV infection. Further exclusion criteria included autoimmune disease, psychiatric disease, uncontrolled diabetes mellitus, symptomatic cardiac or cardiovascular diseases, alcohol intake greater than 20 g daily, and the presence of drug abuse. Patients were ineligible if they had received interferon and/or ribavirin previously. The neutrophil count had to be at least $1.5 \times 10^9$/l, platelet count $>100 \times 10^9$/l, hemoglobin level >120 g/l in women and >130 g/l in men, and serum creatinine levels had to be <1.5 times the upper limit of normal. Decompensated liver cirrhosis (bleeding, ascites, and encephalopathy) and HCC were excluded in all patients by computed tomography (CT) and/or magnetic resonance imaging (MRI) and/or elevated alpha-fetoprotein. Compensated cirrhosis was diagnosed by liver histology or clinical data (CT images). Patients with compensated cirrhosis typically exhibit enlargement of the hilar periportal space, hypertrophy of the caudate lobe and the lateral segment of the left lobe, and atrophy of the right lobe and medial segment of the left lobe on CT images.

To evaluate the efficacy of peginterferon and ribavirin in CHC patients, a matched retrospective cohort study using data on genotype 1 CHC patients derived from our database was conducted. The database included 978 patients who fulfilled the inclusion and exclusion criteria for the period January 2004 to September 2009 at the Department of Infectious Diseases, Second Affiliated Hospital, Harbin Medical University, China. Among the 978 patients, we selected 315 male and 315 female patients using SAS v.8.2 software (SAS Institute, Cary, NC, USA); the match ratio was 1:1. The trial was approved by the Ethics Committee according to the Declaration of Helsinki. All patients gave written informed consent before treatment.

### 2.2. Serum HCV RNA and HCV genotyping

Serum antibodies to HCV were detected using a third-generation HCV enzyme-linked immunosorbent assay (Ortho Diagnostic Systems, Raritan, NJ, USA). Serum HCV RNA levels were measured by a quantitative reverse-transcriptase PCR assay (COBAS Amplicor HCV Monitor 2.0; Roche Diagnostic Systems, Branchburg, NJ, USA) at baseline, at weeks 4, 12, and every 12 weeks thereafter during treatment, at the end of treatment, and at week 24 of follow-up. The lower detection limit of the qualitative assay is 100 copies/ml. The HCV genotype was determined by restriction fragment length polymorphism (RFLP) of sequences amplified in the 5′ non-coding region.

### 2.3. Liver histology

Pretreatment liver biopsy specimens were analyzed for fibrosis according to METAVIR classification on a scale of F0–F4 (F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with a few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis).

### 2.4. Treatment regimen and dose modifications

The patients received 180 μg peginterferon alpha 2a (PEGASYS, Hoffmann to Roche, Basel, Switzerland) subcutaneously once a week plus daily ribavirin (1000 mg/day for weight <75 kg or 1200 mg/day for weight ≥75 kg) for 48 weeks. All subjects were followed up for 24 weeks after cessation of therapy.

Dosage reduction of peginterferon alpha-2a and ribavirin were advised for managing neutropenia, thrombocytopenia, and anemia. The peginterferon alpha-2a dose was modified by a 45-μg stepwise decrease to enhance adherence. When the patient's absolute neutrophil count (ANC) fell below $0.75 \times 10^9$/l, the dose of peginterferon alpha-2a was reduced to 135 or 90 μg per week; when the patient's ANC fell below $0.5 \times 10^9$/l, peginterferon alpha-2a was temporarily discontinued. When the patient's platelet count fell below $50 \times 10^9$/l, the dose of peginterferon alpha-2a was reduced to 90 μg per week; when the patient's platelet count fell below $25 \times 10^9$/l, peginterferon alpha-2a was temporarily discontinued. The dose of ribavirin was reduced by 200 mg/day when the patient's hemoglobin concentration fell below 100 g/l.[15] Ribavirin was discontinued when the patient's hemoglobin concentration fell below 85 g/l. Patients could receive peginterferon alpha-2a alone if ribavirin was stopped. Restoration of the treatment was permitted if laboratory abnormalities improved. The use of granulocyte macrophage colony-stimulating factor (GM-CSF) was permitted to manage hematologic adverse events. Erythropoietin (EPO) was not used to manage anemia in this study, as the use of EPO to manage IFN- and ribavirin induced anemia has not been approved in China.

### 2.5. Observation indicators

Achievement of rapid virologic response (RVR), complete early virologic response (cEVR), partial early virologic response (pEVR), end-of-treatment virologic response (ETVR), and SVR of patients was observed. RVR was defined as undetectable serum HCV RNA after 4 weeks of combination therapy. cEVR was defined as HCV RNA negative at week 12, but no RVR. pEVR was defined as a ≥2 $\log_{10}$ drop in HCV RNA level from baseline at week 12, but no RVR or cEVR. Patients with undetectable virus at the end of treatment were considered to have achieved an ETVR. Relapse was defined as patients with undetectable HCV RNA at the end of treatment and detectable HCV RNA during follow-up. Only patients with undetectable virus at the end of treatment and again 24 weeks

after completion of treatment were considered to have achieved a SVR.

Patients receiving ≥80% of the planned peginterferon alpha-2a or ribavirin dose were recorded. The rate of patients receiving ≥80% of the planned peginterferon alpha-2a or ribavirin dose and virologic response rates (RVR, cEVR, pEVR, ETVR, SVR, and relapse rate) were compared between males and females in three age groups (<40 years, 40–50 years, and 51–60 years).

### 2.6. Statistical analysis

The clinical, biochemical, and virologic characteristics of the patients were expressed as mean ± standard deviation. The Student's *t*-test was used when necessary for statistical comparison of quantitative data, and the Chi-square test or Fisher's exact test was used when necessary for qualitative data. For all analyses a *p*-value of <0.05 was considered statistically significant.

Multiple logistic regression analysis was used to identify factors related to SVR of CHC patients. In the multivariate logistic regression model, the efficacy of combination antiviral therapy (coded as 1, with SVR, or 0, without SVR) was defined as the dependent variable, and several factors (sex, age, HCV RNA levels, alanine aminotransferase (ALT) levels, body weight, body mass index (BMI), hemoglobin levels, white blood cell counts, platelet counts, histological fibrosis, ≥80% of the planned peginterferon alpha-2a dose, ≥80% of the planned ribavirin dose, and RVR) were defined as independent variables. Variables that achieved statistical significance in the univariate analysis (*p*-value <0.05) were subsequently included in a logistic regression analysis. Selection of variables was based on a stepwise regression analysis using a forward selection method. All analyses were performed using statistical software package SPSS, version 10.0 (SPSS Inc., Chicago, IL, USA).

## 3. Results

### 3.1. Characteristics of patients in the three study groups at baseline

The patients were divided into three groups according to age: patients aged <40 years ($n = 200$), patients aged 40–50 years ($n = 210$), and patients aged 51–60 years ($n = 220$). Liver biopsy was performed in 91 patients (45.5%) aged <40 years, 96 patients (45.7%) aged 40–50 years, and 100 patients (45.5%) aged 51–60 years. The remaining patients refused a liver biopsy; they were diagnosed by clinical data. Compensated cirrhosis (Child–Pugh score <6) was present in 51 patients.

The demographic, virologic, and clinical characteristics were similar in the male and female patients (Table 1), except that in the group of patients aged 51–60 years, male patients had a significantly higher mean hemoglobin level (142 ± 15 vs. 135 ± 12 g/l, $t = 3.822$, $p < 0.05$), mean white blood cell count (4.7 ± 0.8 vs. 4.4 ± 0.9 × $10^9$/l, $t = 2.613$, $p < 0.05$), and mean platelet count (159 ± 24 vs. 149 ± 25 × $10^9$/l, $t = 3.026$, $p < 0.05$) than female patients; also, histological fibrosis was more advanced in female patients than male patients (22/12/16 vs. 38/6/6, Chi-square = 10.812, $p = 0.004$) and compensated cirrhosis was more frequent in female patients than male patients (19/60 vs. 8/60, Chi-square = 5.783, $p = 0.016$).

### 3.2. Comparison of the rate of patients receiving ≥80% of the planned drug dose between males and females in the three age groups

The rates of male and female patients receiving ≥80% of the planned drug dose in the different age groups were compared (Table 2). There were no significant differences between male and female patients in the rates receiving ≥80% of the planned peginterferon alpha-2a dose in the three age groups. In the group of

**Table 1**
Characteristics of 630 genotype 1 chronic hepatitis C patients at baseline

| Group | *n* | Age (years) | ALT (U/l) | HCV RNA (log copies/ml) | PLT ($\times 10^9$/l) | WBC ($\times 10^9$/l) | Hb (g/l) | Body weight (kg) | BMI (kg/m$^2$) | Fibrosis (F0–2/F3/F4) | No. of patients with compensated cirrhosis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients aged <40 years | | | | | | | | | | | |
| Male | 100 | 33.5 ± 6.5 | 94 ± 18 | 6.0 ± 1.4 | 172 ± 38 | 5.3 ± 1.2 | 148 ± 19 | 64.2 ± 10.5 | 23.4 ± 2.8 | 39/4/3 | 4 |
| Female | 100 | 33.8 ± 6.7 | 92 ± 19 | 6.1 ± 1.3 | 170 ± 37 | 5.2 ± 1.1 | 147 ± 18 | 63.6 ± 10.4 | 23.2 ± 2.7 | 38/4/3 | 5 |
| Patients aged 40–50 years | | | | | | | | | | | |
| Male | 105 | 45.8 ± 3.4 | 97 ± 20 | 6.2 ± 1.5 | 165 ± 30 | 4.9 ± 1.0 | 145 ± 18 | 63.6 ± 10.3 | 23.3 ± 3.0 | 40/2/6 | 7 |
| Female | 105 | 46.0 ± 3.5 | 98 ± 21 | 6.3 ± 1.6 | 164 ± 31 | 5.0 ± 1.1 | 144 ± 17 | 63.3 ± 10.4 | 23.1 ± 2.9 | 39/3/6 | 8 |
| Patients aged 51–60 years[a] | | | | | | | | | | | |
| Male | 110 | 55.7 ± 5.8 | 85 ± 16 | 6.1 ± 1.4 | 159 ± 24 | 4.7 ± 0.8 | 142 ± 15 | 63.0 ± 10.3 | 23.0 ± 2.5 | 38/6/6 | 8 |
| Female | 110 | 56.0 ± 5.9 | 84 ± 17 | 6.2 ± 1.5 | 149 ± 25 | 4.4 ± 0.9 | 135 ± 12 | 62.2 ± 10.1 | 22.8 ± 2.4 | 22/12/16 | 19 |

Results are mean ± standard deviation. ALT, alanine aminotransferase; HCV, hepatitis C virus; RNA, ribonucleic acid; PLT, platelet count; WBC, white blood cell count; Hb, hemoglobin; BMI, body mass index.

[a] In patients aged 51–60 years: PLT: $t = 3.026$, $p < 0.05$; WBC: $t = 2.613$, $p < 0.05$; Hb: $t = 3.822$, $p < 0.05$; fibrosis: Chi-square = 10.812, $p = 0.004$; compensated cirrhosis: Chi-square = 5.783, $p = 0.016$.

**Table 2**
Comparison of the rate of patients receiving ≥80% of the planned drug dose between males and females in the different age groups

| | Male | Female | *p*-Value |
|---|---|---|---|
| Patients aged <40 years | | | |
| ≥80% of planned peginterferon dose | 90% (90/100) | 92% (92/100) | Chi-square = 0.244, $p = 0.621$ |
| ≥80% of planned ribavirin dose | 88% (88/100) | 85% (85/100) | Chi-square = 0.385, $p = 0.535$ |
| Patients aged 40–50 years | | | |
| ≥80% of planned peginterferon dose | 83.8% (88/105) | 81.0% (85/105) | Chi-square = 0.295, $p = 0.587$ |
| ≥80% of planned ribavirin dose | 79.0% (83/105) | 76.2% (80/105) | Chi-square = 0.247, $p = 0.619$ |
| Patients aged 51–60 years | | | |
| ≥80% of planned peginterferon dose | 74.5% (82/110) | 70% (77/110) | Chi-square = 0.567, $p = 0.451$ |
| ≥80% of planned ribavirin dose | 61.8% (68/110) | 42.7% (47/110) | Chi-square = 8.035, $p = 0.005$ |

patients aged 51–60 years, the rate of patients receiving ≥80% of the planned ribavirin dose was significantly lower in females than in males (42.7%, 47/110 vs. 61.8%, 68/110; Chi-square = 8.035, $p = 0.005$).

### 3.3. Comparison of the rate of patients receiving GM-CSF between males and females in the three age groups

One hundred and thirty-one patients received GM-CSF during treatment. In patients aged <40 years, the rate of patients receiving GM-CSF was 9% (9/100) in male patients and 12% (12/100) in female patients, showing no significant difference (Chi-square = 0.479, $p = 0.489$). In patients aged 40–50 years, the rate of patients receiving GM-CSF was 14.4% (15/105) in male patients and 17.1% (18/105) in female patients, showing no significant difference (Chi-square = 0.324, $p = 0.569$). In patients aged 51–60 years, the rate of patients receiving GM-CSF was significantly higher in females than in males (42.7%, 47/110 vs. 27.3%, 30/110; Chi-square = 5.774, $p = 0.005$).

### 3.4. Comparison of virologic response rates between males and females in the three age groups

In the group of patients aged <40 years, the pEVR rate of males was significantly higher than that of females (38%, 38/100 vs. 17%, 17/100; Chi-square = 11.060, $p = 0.001$); there was no significant difference in the ETVR rate between males and females (80%, 80/100 vs. 85%, 85/100; Chi-square = 0.866, $p = 0.352$); the relapse rate of males was significantly higher than that of females (32.5%, 26/80 vs. 11.8%, 10/85; Chi-square = 10.388, $p = 0.001$); the SVR rate of females was significantly higher than that of males (75%, 75/100 vs. 54%, 54/100; Chi-square = 9.630, $p = 0.002$) (Table 3).

In the group of patients aged 40–50 years, there was no significant difference in the ETVR rate (80%, 84/105 vs. 82.9%, 87/105; Chi-square = 0.283, $p = 0.594$), the relapse rate (36.9%, 31/84 vs. 34.5%, 30/87; Chi-square = 0.109, $p = 0.741$), or the SVR rate (50.5%, 53/105 vs. 54.3%, 57/105; Chi-square = 0.305, $p = 0.580$) between males and females (Table 4).

In the group of patients aged 51–60 years, the pEVR rate of males was significantly lower than that of females (26.4%, 29/110 vs. 46.4%, 51/110; Chi-square = 9.507, $p = 0.002$); the relapse rate of males was significantly lower than that of females (36.9%, 31/84 vs. 54.3%, 44/81; Chi-square = 5.045, $p = 0.025$); there was no significant difference in the ETVR rate between males and females (76.4%, 84/110 vs. 73.6%, 81/110; Chi-square = 0.218, $p = 0.640$); the SVR rate of females was significantly lower than that of males (33.6%, 37/110 vs. 48.2%, 53/110; Chi-square = 4.814, $p = 0.028$) (Table 5).

### 3.5. Comparison of SVR rates between males and females in patients receiving ≥80% of the planned drug dose

To exclude the effects of drug dose reductions on virologic response rates, we further investigated the SVR rates between

**Table 3**
Comparison of virologic response rates between male and female patients aged <40 years

| Group | n | On-treatment virologic response | | | | ETVR[b] | Relapse rate[c] | SVR[d] |
|---|---|---|---|---|---|---|---|---|
| | | RVR | cEVR | pEVR[a] | No RVR or EVR | | | |
| Male | 100 | 16% (16/100) | 30% (30/100) | 38% (38/100) | 16% (16/100) | 80% (80/100) | 32.5% (26/80) | 54% (54/100) |
| Female | 100 | 20% (20/100) | 48% (48/100) | 17% (17/100) | 15% (15/100) | 85% (85/100) | 11.8% (10/85) | 75% (75/100) |

RVR, rapid virologic response; cEVR, complete early virologic response; pEVR, partial early virologic response; ETVR, end of treatment virologic response; SVR, sustained virological response.
[a] pEVR: Chi-square = 11.060, $p = 0.001$.
[b] ETVR: Chi-square = 0.866, $p = 0.352$.
[c] Relapse rate: Chi-square = 10.388, $p = 0.001$.
[d] SVR: Chi-square = 9.630, $p = 0.002$.

**Table 4**
Comparison of virologic response rates between male and female patients aged 40–50 years

| Group | n | On-treatment virologic response | | | | ETVR[a] | Relapse rate[b] | SVR[c] |
|---|---|---|---|---|---|---|---|---|
| | | RVR | cEVR | pEVR | No RVR or EVR | | | |
| Male | 105 | 16.2% (17/105) | 28.6% (30/105) | 39.0% (41/105) | 16.2% (17/105) | 80% (84/105) | 36.9% (31/84) | 50.5% (53/105) |
| Female | 105 | 19.0% (20/105) | 33.3% (35/105) | 27.6% (29/105) | 20% (21/105) | 82.9% (87/105) | 34.5% (30/87) | 54.3% (57/105) |

RVR, rapid virologic response; cEVR, complete early virologic response; pEVR, partial early virologic response; ETVR, end of treatment virologic response; SVR, sustained virological response.
[a] ETVR: Chi-square = 0.283, $p = 0.594$.
[b] Relapse rate: Chi-square = 0.109, $p = 0.741$.
[c] SVR: Chi-square = 0.305, $p = 0.580$.

**Table 5**
Comparison of virologic response rates between male and female patients aged 51–60 years

| Group | n | On-treatment virologic response | | | | ETVR[b] | Relapse rate[c] | SVR[d] |
|---|---|---|---|---|---|---|---|---|
| | | RVR | cEVR | pEVR[a] | No RVR or EVR | | | |
| Male | 110 | 18.2% (20/110) | 36.4% (40/110) | 26.4% (29/110) | 19.1% (21/110) | 76.4% (84/110) | 36.9% (31/84) | 48.2% (53/110) |
| Female | 110 | 15.5% (17/110) | 18.2% (20/110) | 46.4% (51/110) | 20% (22/110) | 73.6% (81/110) | 54.3% (44/81) | 33.6% (37/110) |

RVR, rapid virologic response; cEVR, complete early virologic response; pEVR, partial early virologic response; ETVR, end of treatment virologic response; SVR, sustained virological response.
[a] pEVR: Chi-square = 9.507, $p = 0.002$.
[b] ETVR: Chi-square = 0.218, $p = 0.640$.
[c] Relapse rate: Chi-square = 5.045, $p = 0.025$.
[d] SVR: Chi-square = 4.814, $p = 0.028$.

**Table 6**
Univariate analysis of factors influencing SVR in chronic hepatitis C patients

| Variable | With an SVR ($n$ = 329) | Without an SVR ($n$ = 301) | $p$-Value |
|---|---|---|---|
| Sex (male/female) | | | Chi-square = 6.167, $p$ = 0.046 |
| Patients aged <40 years | 54/75 | 46/25 | |
| Patients aged 40–50 years | 53/57 | 52/48 | |
| Patients aged 51–60 years | 53/37 | 57/73 | |
| Age (years), mean ± SD | 46.8 ± 4.7 | 49.5 ± 5.4 | Chi-square = 6.670, $p$ = 0.003 |
| Presence of RVR | 90/239 | 20/281 | Chi-square = 46.786, $p < 0.001$ |
| HCV RNA ($\log_{10}$ copies/ml) | 5.5 ± 0.8 | 6.4 ± 0.9 | $t$ = 13.382, $p$ = 0.001 |
| ALT level (U/l) | 92 ± 16 | 94 ± 17 | $t$ = 1.517, $p$ = 0.120 |
| Body weight (kg) | 63.4 ± 10.4 | 63.8 ± 10.6 | $t$ = 0.477, $p$ = 0.439 |
| BMI (kg/m$^2$) | 23.3 ± 3.0 | 23.1 ± 2.9 | $t$ = 0.850, $p$ = 0.121 |
| Platelet count ($\times 10^9$/l) | 167 ± 30 | 162 ± 29 | $t$ = 2.126, $p$ = 0.040 |
| White blood cell count ($\times 10^9$/l) | 4.8 ± 1.2 | 4.7 ± 1.1 | $t$ = 1.090, $p$ = 0.363 |
| Hemoglobin level (g/l) | 143 ± 18 | 141 ± 20 | $t$ = 1.289, $p$ = 0.171 |
| ≥80% of planned peginterferon alfa-2a dose (yes/no) | 274/55 | 240/61 | Chi-square = 1.318, $p$ = 0.251 |
| ≥80% of planned ribavirin dose (yes/no) | 255/74 | 196/105 | Chi-square = 11.866, $p$ = 0.001 |
| Histological fibrosis (F0–2/F3–4) | 144/32 | 72/39 | Chi-square = 10.508, $p$ = 0.001 |

SVR, sustained virologic response; SD, standard deviation; RVR, rapid virologic response; HCV, hepatitis C virus; RNA, ribonucleic acid; ALT, alanine aminotransferase; BMI, body mass index.

male and female patients who received ≥80% of the planned peginterferon alpha-2a or ribavirin dose. In patients aged 51–60 years, 159 patients received ≥80% of the planned peginterferon alpha-2a dose and the SVR rate of females was significantly lower than that of males (42.9%, 33/77 vs. 61.0%, 50/82; Chi-square = 5.225, $p$ = 0.022); 115 patients received ≥80% of the planned ribavirin dose and the SVR rate of females was significantly lower than that of males (38.3%, 18/47 vs. 64.7%, 44/68; Chi-square = 7.800, $p$ = 0.005).

### 3.6. The role of RVR in predicting SVR

The SVR rate (81.8%, 90/110) in patients who had achieved RVR was significantly higher than in those who had not (46.0%, 239/520) (Chi-square = 46.786, $p < 0.001$). In patients aged <40 years, the positive predictive value of RVR in males was 81.3% (13/16) and in females was 80% (16/20), showing no significant difference between them (Chi-square = 0.009, $p$ = 0.925). In patients aged 40–50 years, the positive predictive value of RVR in males was 82.4% (14/17) and in females was 85% (17/20), showing no significant difference between them (Chi-square = 0.047, $p$ = 0.828). In patients aged 51–60 years, the positive predictive value of RVR in males was 80% (16/20) and in females was 82.4% (14/17), showing no significant difference between them (Chi-square = 0.033, $p$ = 0.855).

### 3.7. Predictive factors associated with SVR in CHC patients

Predictive factors associated with SVR in CHC patients were studied. In univariate analysis, age ($p$ = 0.003), HCV RNA levels ($p$ = 0.001), sex ($p$ = 0.046), platelet counts ($p$ = 0.040), histological fibrosis ($p$ = 0.001), ≥80% of the planned ribavirin dose ($p$ = 0.001), and the presence of RVR ($p < 0.001$) were associated with SVR (Table 6). However, in multivariate logistic regression analysis, the independent factors associated with SVR were age ($p$ = 0.015), sex ($p$ = 0.002), ≥80% of the planned ribavirin dose ($p$ = 0.006), and the presence of RVR ($p$ = 0.001) (Table 7).

### 3.8. Predictive factors associated with SVR in patients aged 51–60 years

To identify patients aged 51–60 years who may benefit from combination therapy, we determined factors associated with SVR. In univariate analysis, sex ($p$ = 0.028), HCV RNA levels ($p$ = 0.009), histological fibrosis ($p$ = 0.033), ≥80% of the planned ribavirin dose ($p$ = 0.029), and the presence of RVR ($p < 0.001$) were associated with SVR (Table 8). However, in multivariate logistic regression analysis, the independent factors associated with SVR were sex ($p$ = 0.013), ≥80% of the planned ribavirin dose ($p$ = 0.008), and presence of RVR ($p$ = 0.001) (Table 9).

## 4. Discussion

It is notable that not only age but also sex might play a role in influencing the efficacy of treatment in patients with CHC. To date, the difference in response to treatment in patients with CHC according to gender is controversial.[11–14] The greatest physiological change in women with increasing age is a decreased serum concentration of estrogen after they enter the menopause.[16] During the perimenopause (from age 40 years), ovulation can be erratic, and plasma gonadotropin levels frequently reach menopausal levels, even when plasma estrogen levels are within the menstrual range.[17] Experimental data suggest that estrogens may have an antifibrotic effect. The antiviral therapeutic effects decrease with aging in female patients. Therefore, we evaluated the effect of gender on the treatment of CHC patients categorized by age.

**Table 7**
Multivariate logistic regression analysis of factors influencing SVR in chronic hepatitis C patients

| Variable | Coefficient | Chi-square | OR (95% CI) | $p$-Value |
|---|---|---|---|---|
| Age | 1.523 | 4.931 | 4.586 (2.104–5.754) | 0.015 |
| Presence of RVR | 2.103 | 15.167 | 8.191 (4.186–9.983) | 0.001 |
| Sex | 1.123 | 12.005 | 3.074 (2.103–4.756) | 0.002 |
| HCV RNA levels | 1.314 | 3.048 | 3.721 (2.403–4.996) | 0.063 |
| Histological fibrosis | 1.754 | 2.617 | 5.778 (2.586–7.998) | 0.109 |
| ≥80% of planned ribavirin dose | 2.431 | 11.001 | 11.370 (5.279–16.025) | 0.006 |
| Platelet count | 1.017 | 2.566 | 2.765 (2.000–5.016) | 0.095 |

SVR, sustained virologic response; OR, odds ratio; CI, confidence interval; RVR, rapid virologic response; HCV, hepatitis C virus; RNA, ribonucleic acid.

**Table 8**
Univariate analysis of factors influencing SVR in patients aged 51–60 years

| Variable | With an SVR ($n=90$) | Without an SVR ($n=130$) | $p$-Value |
|---|---|---|---|
| Sex (male/female) | 53/37 | 57/73 | Chi-square = 4.814, $p=0.028$ |
| Presence of RVR | 30/60 | 7/123 | Chi-square = 29.695, $p<0.001$ |
| HCV RNA (log copies/ml) | $5.8\pm0.9$ | $6.4\pm1.0$ | $t=4.644$, $p=0.009$ |
| ALT level (U/l) | $91\pm18$ | $93\pm17$ | $t=0.829$, $p=0.342$ |
| Age (years), mean ± SD | $55.4\pm4.5$ | $55.8\pm4.4$ | $t=0.654$, $p=0.653$ |
| Body weight (kg) | $62.5\pm10.2$ | $62.4\pm10.1$ | $t=0.068$, $p=0.956$ |
| BMI (kg/m$^2$) | $22.9\pm2.6$ | $22.7\pm2.8$ | $t=0.544$, $p=0.237$ |
| ≥80% of planned peginterferon alfa-2a dose (yes/no) | 64/26 | 95/35 | Chi-square = 0.103, $p=0.749$ |
| ≥80% of planned ribavirin dose (yes/no) | 55/35 | 60/70 | Chi-square = 4.769, $p=0.029$ |
| Histological fibrosis (F0–2/F3–4) | 37/16 | 23/24 | Chi-square = 4.523, $p=0.033$ |
| Platelet count ($\times10^9$/l) | $158\pm27$ | $155\pm26$ | $t=0.823$, $p=0.473$ |
| White blood cell count ($\times10^9$/l) | $4.4\pm0.9$ | $4.2\pm0.8$ | $t=1.695$, $p=0.085$ |
| Hemoglobin level (g/l) | $140\pm17$ | $138\pm16$ | $t=0.879$, $p=0.249$ |

SVR, sustained virologic response; RVR, rapid virologic response; HCV, hepatitis C virus; RNA, ribonucleic acid; ALT, alanine aminotransferase; SD, standard deviation; BMI, body mass index.

**Table 9**
Multivariate logistic regression analysis of factors influencing SVR in patients aged 51–60 years

| Variable | Coefficient | Chi-square | OR (95% CI) | $p$-Value |
|---|---|---|---|---|
| Presence of RVR | 2.001 | 14.003 | 7.396 (4.947–9.998) | 0.001 |
| HCV RNA levels (log copies/ml) | 1.553 | 3.082 | 4.726 (2.003–5.847) | 0.072 |
| Sex | 1.335 | 4.589 | 3.799 (2.009–5.978) | 0.013 |
| ≥80% of planned ribavirin dose | 2.534 | 9.856 | 12.604 (4.853–17.135) | 0.008 |
| Histological fibrosis | 1.210 | 1.756 | 3.353 (0.956–5.867) | 0.282 |

SVR, sustained virologic response; OR, odds ratio; CI, confidence interval; RVR, rapid virologic response; HCV, hepatitis C virus; RNA, ribonucleic acid.

Our study showed that the SVR rate decreased significantly with age in female patients with genotype 1 CHC, and was markedly reduced in patients aged 51–60 years. Our study found that in patients aged <40 years, the SVR rate in females was higher than that in males. The favorable therapeutic effect may be related to high levels of estrogen in these women. It has been proposed that estrogen may suppress hepatic fibrosis through an effect that depends on its hepatic tissue receptors, and improve the antiviral therapy.[18]

To identify factors that predict SVR among patients aged 51–60 years (hard-to-treat population), we studied the factors influencing SVR by multiple logistic regression analysis and found some independent factors associated with SVR, such as sex, ≥80% of the planned ribavirin dose, and the presence of RVR.

Ribavirin accumulates in erythrocytes and induces hemolytic anemia. Older female patients are less resistant to the anemia induced by ribavirin.[19] In our study, in patients aged 51–60 years, female patients had a significantly lower mean hemoglobin level than male patients at baseline, which would have been responsible for the lower rate of patients receiving ≥80% of the planned ribavirin dose in women than in men. To exclude the effects of drug dose reductions on virologic response rates, we further investigated the SVR rates in male and female patients receiving ≥80% of the planned peginterferon alpha-2a or ribavirin dose. We found that the SVR rate of female patients aged 51–60 years was still significantly lower than that of male patients. We found that these female patients had significantly lower mean white blood cell counts and platelet counts than male patients and that the fibrosis stage was more advanced in female patients than in male patients.

We showed that older women have a lower SVR rate and higher relapse rate than men. The lower cumulative ribavirin exposure and decreased antifibrotic effects of low estrogen levels in female patients aged >50 years would produce a lower response to PEG-IFN and ribavirin. The lower cumulative drug exposure to ribavirin due to a higher incidence of hemolytic anemia in older female patients may first explain the higher relapse rate and lower SVR. Increasing rates of bridging fibrosis in women with age may also play a role in reducing the sustained response to combination therapy.

In this study, erythropoietin (EPO) was not used to manage anemia. Recently, EPO therapy has been shown to reduce the risk and magnitude of anemia, and provide space for a higher ribavirin dose.[20] The use of EPO to manage IFN- and ribavirin-induced anemia has not been approved in China. It would be useful to study whether or not this intervention improves the efficacy of treatment.

We found that compared with male patients, the pEVR and relapse rate in older female patients with HCV genotype 1 were high. For elderly patients with pEVR, 48-week combination treatment was not enough to clear HCV. These patients with pEVR might benefit from prolongation of therapy from 48 to 72 weeks. This benefit could derive from a lower relapse rate after the extension of the plasma HCV RNA-free period in slower responders.

The assessment of virological response at treatment week 4 is a simple and reliable tool for identifying patients most likely to achieve an SVR.[21] We found that RVR could predict SVR in a similar way in both male and female patients. Attainment of an RVR is the most powerful predictor of SVR, irrespective of sex.

In conclusion, this study indicates that for genotype 1 CHC, in patients aged <40 years the SVR rate in females is higher than that in males; in patients aged 40–50 years, similar SVR rates are found in males and females; and in patients aged 51–60 years, the SVR rate in females is lower than that in males. Our study was retrospective, and the number of patients in the study population was limited. Thus, a multicenter, randomized and controlled trial is needed to further validate these conclusions.

*Conflict of interest:* No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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