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SVR Rates of HCV-infected population under PEG-IFN- α /R treatment in Northwest China

Yanhua Li^{1†}, Jiuping Wang^{2†}, Juan Wang¹, Yunfeng Xiao³, Bin Xu⁴, Hongwei Li¹, Liu Yang¹, Xiaoke Hao^{1*} and Yueyun Ma^{1*}

Abstract

Background: Chronic HCV Patients taking PEG-IFN- α /R from different ethnic groups have different probabilities of reaching a sustained viral response (SVR). There are many influence factors, such as HCV genotype, IL-28B single-nucleotide polymorphisms (SNP), Fibrosis 4 index (FIB-4), and aspartate aminotransferase-to-platelet ratio index (APRI) score. But the baseline factors in relation to treatment outcome was still not much clear.

Methods: We evaluated data from 231 chronic HCV patients with or without liver fibrosis and their antiviral efficacy after treatment with pegylated interferon plus ribavirin (PEG-IFN- α /R) for 24–48 weeks. IL-28B SNP and HCV genotypes were analyzed with genome sequencing using pyrosequencing.

Results: Sustained viral response (SVR) rates of patients with HCV 1b and 2a genotypes were 52.25% (58/111) and 75.28% (67/89) ($P < 0.01$). SVR rates of patients with IL-28B rs8099917 TT, rs12979860 CC and rs12980275 AA were 92.41% (25/27), 92.86% (26/28) and 88.89% (24/27) separately. We found that SVR rates in HCV 1b and 2a patients were only 31.0 and 39.4% if their FIB-4 > 3.25 . In addition, when their APRI > 2 , only 30.3% of HCV 1b patients and 50.2% of HCV 2a patients could obtain SVR.

Conclusions: There were high proportion of HCV genotype 1b and 2a in Northwest China. In both HCV 1b and 2a genotypes, patients with protective-genotype of IL-28B were more likely to obtain SVR. However, those with significant fibrosis or cirrhosis were less likely, no matter their genotype. Combined factors of HCV genotype, IL-28B genotype, FIB-4 and ARPI may indicate high prediction and clinical value regarding treatment with PEG-IFN- α /R and prognostic evaluation of chronic hepatitis C patients.

Keywords: Chronic hepatitis C, Interleukin 28, Single nucleotide polymorphism, HCV subtype, Cirrhosis, Individualization

Background

Hepatitis C is an infectious disease that is widely spread geographically. It has been reported that about 180 million people are infected with the hepatitis C virus (HCV) worldwide, accounting for about 3% of the current population [1]. The incidence of infection can be easily neglected and thus may develop into cirrhosis and even HCV-related hepatocarcinoma and liver failure, which pose serious threats to human health. More than

0.35 million people have died from HCV-related liver disease [2]. The application of pegylated interferon (PEG-IFN)- α combined with ribavirin (PEG-IFN- α /R) had been considered to be the most popular and effective therapy in blocking virus replication before 2015 [3]. While the novel sofosbuvir-ledipasvir opened a new time for treatment of eligible HCV-infected patients with 90–100% efficiency [4, 5]. Unfortunately sofosbuvir is much more expensive, with an estimated cost of an additional \$65 billion during the next 5 years [6]. It should be carefully thought about the necessity and how much people have to take DAA drugs. And it is not the time to ignore the application of PEG-IFN- α /R, especially in China.

* Correspondence: haoxkg@fmmu.edu.cn; cmbmayy@fmmu.edu.cn

†Equal contributors

¹Department of Clinical Laboratory Medicine, Xijing Hospital, The Fourth Military Medical University, 169 Changle West Road, Xi'an, Shaanxi 710032, People's Republic of China

Full list of author information is available at the end of the article



Patients taking PEG-IFN- α /R from different ethnic groups have different probabilities of reaching a sustained viral response (SVR). In the United States, the rate of obtaining SVR in the black population is almost 50% less than of white patients, and the probability of obtaining SVR in white patients with HCV genotype 1 treated by PEG-IFN- α /R is approximately 42–53% [7]. In China, the SVR rate was a little higher, could reach 65.3% [8]. We recently found that northwest patients of China seem to have higher SVR that was 72.6%. Because there were seldom immigrant in the northwest population, the high SVR is reasonable caused by geographic specificity, such as genotype of HCV and polymorphisms of IL-28B.

Determination of HCV genotype is important to predict response to antiviral therapy and time of treatment [9]. Early clinical trials have reported that SVR rates for patients with genotype 1 (42–46%) are lower than rates for patients with non-type 1 genotype (76–82%) [10]. On the other hand, genome-wide association studies have suggested that host IL-28B single-nucleotide polymorphisms (SNP) rs12979860 CC and rs8099917 TT are significantly correlated with SVR in patients receiving PEG-IFN- α /R treatment [11]. The probability of obtaining SVR is further reduced in vivo if IL-28B is mutated in patients with HCV genotype 1 infection [12, 13].

Liver fibrosis had been suggested being closely associated with the risk of HCC development in chronic hepatitis C patients [14]. The eradication of HCV with antiviral therapy will prevent the progression of chronic hepatitis and associated complications [15]. But it was never paid more attention in China [8].

To determine the favorable patients for treatment with PEG-IFN- α /R, HCV genotype, IL-28B SNP, Fibrosis 4 (FIB-4) index and aminotransferase-to-platelet ratio index (APRI) score we retrospectively analyzed with SVR in this study.

Methods

Patients

All patients with CHC were enrolled for this research with signed informed consents following the protocols approved by the Institutional Review Board of the Fourth Military Medical University (Table 1). Inclusion criteria: patients were firstly diagnosed as HCV infection since August 2013, naive-treatment from October 2013 and HCV RNA > 1000 IU/mL. Exclusion criteria: Patients with recurrence of hepatitis C, hepatitis infected with HAV, HBV, HDV, HEV, EBV or CMV; HIV infection, Diabetes, autoimmune liver disease and HCC etc. were excluded.

We collected data on 230 patients with chronic HCV infection who were seen at Xijing Hospital from October 2013 to February 2016. The average age was 46.71 years (range, 20–80 y), with 112 male and 118 female patients. Patients had been treated with standard of care for 24–48 weeks. PEG IFN- α /RBV: The recommended dose of PEG IFN- α 2a (Pegasys Roche Shanghai) for chronic hepatitis C was 180 μ g per time, once a week, subcutaneous injection of the abdomen or thigh. The dose of RBV was determined by the genotype of virus: the dose for genotype 2 or 3 was 800 mg a day for 24 weeks, and the dose of genotype 1 was 1000–1200 mg daily according to body weight, for 48 weeks. We mainly investigated outcomes after 24 weeks.

There are many serological markers for HCV or evidence of liver disease including HCV RNA was used to understand the activity of virus replication, ALT, AST, Total bilirubin, direct bilirubin, indirect bilirubin, albumin, globulin, choline esterase, alkaline phosphatase, phosphatase and abdominal ultrasound were used for evaluation of liver damage, CT or MRI was used to be clear of the extent of liver damage. Liver biopsy is the gold standard for evaluation of liver inflammation and

Table 1 Clinical characteristic of patients with different HCV genotypes

HCV Genotype	No.	Age (y), range	Sex (No. of Patients, %)		Viral load (10^6 IU/mL), range	ALT (U/L), range	AST (U/L), range
			Male	Female			
1a	12	39.67 (24–60)	7 (58.33)	5 (41.67)	2.33 (0.01–29.90)	58.17 (19–249)	37.08 (10–157)
1b	111	46.81 (20–79)	52 (47.27)	58 (52.73)	1.62 (0.02–46.1)	50.15 (13–392)	44.96 (16–453)
2a	89	50.45 (22–80)	40 (44.94)	49 (55.06)	2.60 (0.00–18.10)	49.38 (12–554)	35.25 (15–205)
2b	1	54.00 (54–54)	0 (100.00)	1 (0.00)	1.08	286.00	351.00
3a	11	37.91 (25–53)	8 (72.73)	3 (27.27)	5.52 (0.21–29.5)	91.27 (37–340)	50.36 (32–160)
3b	5	38.00 (23–45)	3 (60.00)	2 (40.00)	1.71 (0.10–6.88)	52.40 (58–204)	37.00 (44–141)
4a	0						
5a	1	43.00 (43–43)	2 (100.00)	0 (0.00)	0.00	0.00	0.00
6a	1	25.00 (25–25)	1 (100.00)	0 (0.00)	0.00	0.00	0.00
		Z = 3.6464	chi-squared = 0.643		Z = 1.8797	Z = 0.6820	Z = 0.6820
P value		.067	.836		.113	.605	.605

The low number of patients with 2b, 4a, 5a and 6a did not meet the statistical requirements; therefore, these were excluded for follow-up statistics

fibrosis staging in patients. In addition, there were also patient compliance issues. After careful consideration we chose these common and easy to get markers as ALT and AST for liver damage, FIB-4 and APRI to evaluate liver fibrosis. Use of viral content to evaluate curative effect was according to the 2014 European Association for the Study of the Liver Recommendations on Treatment of Hepatitis C and the Guideline of Prevention and Treatment of Hepatitis C [16, 17]. We evaluated SVR using quantitative real-time fluorescence polymerase chain reaction (ViiA7 OX, Life Technology) of HCV RNA (less than 15 IU/mL) for at least 24 weeks of follow-up at the end of treatment. Samples were collected and separated from the peripheral blood and serum and then stored at -20°C until analyses.

DNA/RNA extraction

For DNA extraction for IL-28B gene detection, we used a blood genomic DNA extraction kit (Tiangen, Beijing, China). For HCV RNA extraction, we used the MinElute column QIAamp method and the virus genome DNA/RNA extraction kit (Tiangen). All extracted DNA/RNA were then immediately used for gene detection or stored at -80°C .

Quantitative real-time fluorescence PCR

Primer sequences were designed by using DNAMAN 6.0.3.99 (LynnonBiosoft, San Ramon, CA, US) for IL-28B gene amplification, including IL-28B rs8099917, IL-28B rs12979860 and IL-28B rs12980275 genes (Table 2). Among them, 5' of 3 reversed primers were labeled with biotin. Amplification included heating at 95°C for 5 min, 95°C for 20 s, and 60°C for 20 s, with steps repeated for 40 cycles. Amplification was run on a 7500 fast real-time PCR system (Applied Biosystems, Foster City, CA, USA). HCV genotype was measured by using an HCV genotyping PCR kit (Qiagen, Beijing, China), following the manufacturer's protocol.

Table 2 Primers for genotype analysis of IL-28B

Primer	IL-28B	Sequence
RT-PCR primers	rs12989760 forward:	5'-GTCGTGCTGCTGCTGACTGA-3'
	rs12989760 reverse:	5'-AGCGCGGAGTGCAATTCA-3'
	rs8099917 forward:	5'-CTCCTTTTGTITTTCTTCTGTGA-3'
	rs8099917 reverse:	5'-ACATAAAAAGCCAGCTACCAA-3'
	rs12980275 forward:	5'-ACATGAGGTGCTGAGAGAAGTCAA-3'
	rs12980275 reverse:	5'-TACCCCGCAATATTTAGACAC-3'
Sequencing primers	rs12989760	5'-AGTCCCCGAAGGCG-3'
	rs8099917:	5'-TCCTTTCTGTGCAAT-3'
	rs12980275:	5'-GAAGTCAAATCTAGAAA-3'

Gene sequencing

IL-28B gene polymorphism was detected with the use of a pyrosequencing method on Q24MDX (Qiagen, Hilden, Germany). Sequencing primers were designed by the Q24 PyroMark. HCV polymorphism sequencing primers were also provided by Qiagen.

Liver fibrosis staging

The degree of liver fibrosis was evaluated with APRI score, which can be used for the assessment of liver cirrhosis [18]. APRI scores >2 in adults indicate that the patient has already had liver cirrhosis. The APRI score is calculated as follows: (aspartate aminotransferase [AST]/ULN) \times 100/platelets ($10^9/\text{L}$), where ULN is the upper limit of normal value. Fibrosis-4 index was based on values of ALT, AST, platelet count and patient age. This index can be used to diagnose liver fibrosis (similar to least significant fibrosis using METAVIR F scoring system ≥ 2) [19]. A significant liver fibrosis has occurred if a patient shows a FIB-4 index of >3.25 . FIB-4 is calculated as follows: age \times ALT (IU/L)/(platelet count [$10^9/\text{L}$] \times AST [IU/L])^{1/2}.

Statistical analyses

We used Pearson chi-squared and Kruskal-Wallis tests to analyze the qualitative data with SPSS 19.0 (IBM, USA.). A logistic regression model was used to analyze the correlation between SNPs (IL-28B rs8099917, IL-28B rs12979860 and IL-28B rs12979860) and SVR of patients. Odds ratio (OR) was used to describe the correlating degree of disease and exposed factors. OR tests were two-sided tests, in which $P < 0.05$ was considered to be statistically significant.

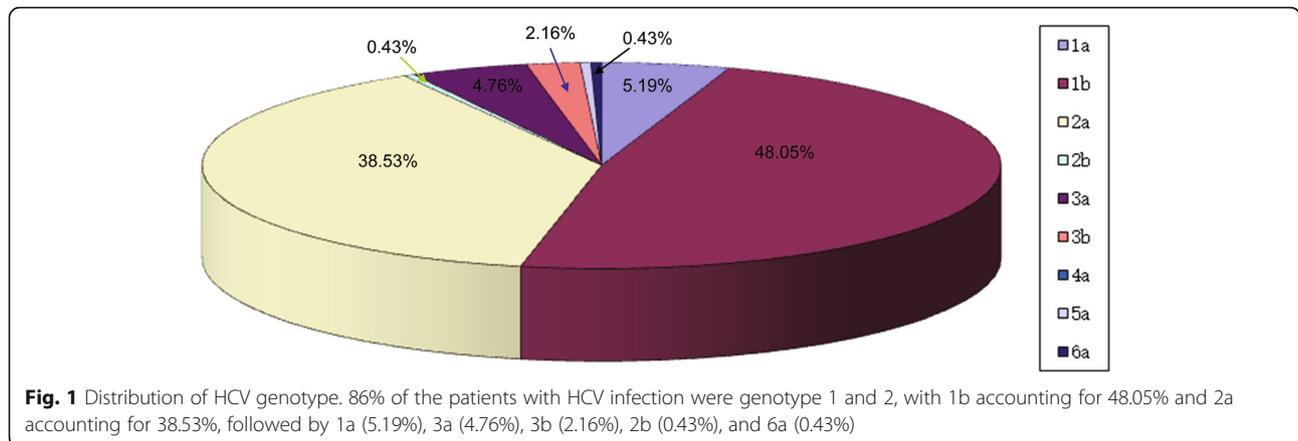
Results

HCV genotype and distribution

HCV genotypes of 230 patients with chronic HCV infection were sequenced, with results shown in Table 2. One patient had mixed infection of 1b and 5a. For statistical analyses, this patient was analyzed in both the 1b and 5a genotype groups. Statistical results of 1a, 1b, 2a, 2b, 3a, 3b, 4a, 5a and 6a genotypes are presented in Fig. 1. The ratio of genotypes were as follows: 5.19% with 1a (12/230), 48.05% with 1b (111/230), 38.53% with 2a (89/230), 0.43% with 2b (1/230), 4.76% with 3a (11/230), 2.16% with 3b (5/230), 0% with 4a (0/230), 0.43% with 5a (1/230), and 0.43% with 6a (1/230). There were no significant differences in age, sex, viral load and alanine aminotransferase (ALT) and aspartate transaminase (AST) levels ($P > 0.05$).

IL-28B genotype in patients with chronic HCV infection

Fifty-one patients with HCV were included in the IL-28B gene polymorphism loci analyses (Table 3). Of the IL-28B genotypes, 76.47% of patients were



rs8099917 TT, 76.47% were rs12979860 CC, and 72.55% were rs12980275 AA. We also found that 5.88% of the IL-28B genotypes were rs8099917 GG, rs12979860 TT or rs12980275 GG. Details of clinical features are presented in Table 3. Statistical results showed no statistical differences in age, sex, viral load and ALT and AST levels ($P > 0.05$).

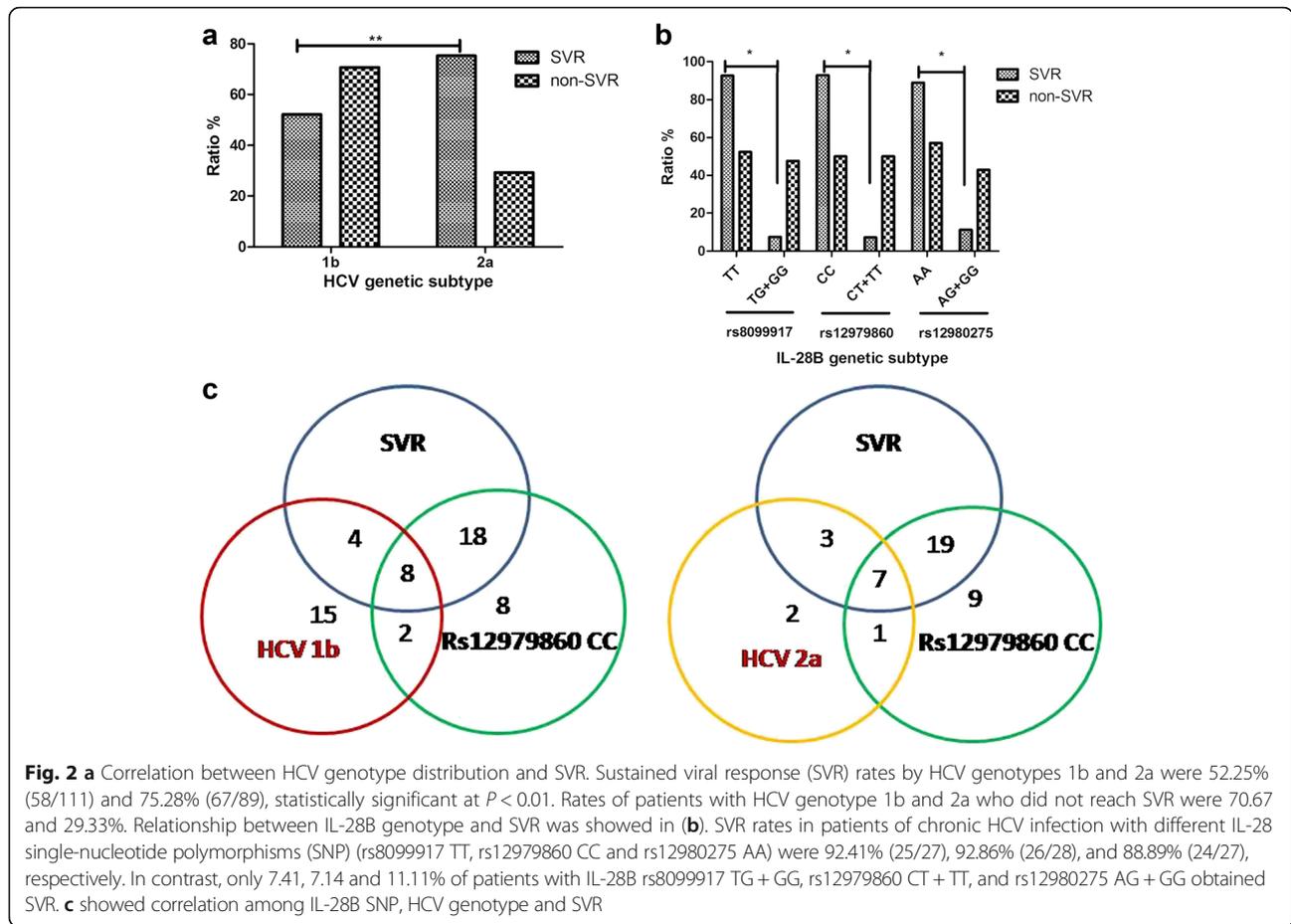
Correlation between HCV genotypes and antiviral efficacy
 HCV genotypes 1b and 2a accounted for 86% of all samples; therefore, we mainly evaluated the correlation between these 2 genotypes and antiviral efficacy. SVR rates in patients with HCV genotype 1b and HCV genotype 2a were 52.25% (58/111) and 75.28% (67/89), with differences being statistically significant (chi-squared = 21.56; $P < 0.01$). In patients with HCV genotype 1b, 70.67% (53/75) did not reach SVR (Fig. 2a).

Role of IL-28B gene polymorphism in antiviral efficacy

We used SNP Stats Software (<http://bioinfo.iconcolgia.net/snpstats/start.htm> [13]) for correlation analyses. After adjusting for confounding factors (including age, sex, viral load, ALT and AST), we found that there was a correlation between patients with SVR and IL-28B genotype ($P < 0.05$), with OR (95% confidence interval) of 11.02 (3.98–23.16) for rs8099917, 10.20 (5.23–22.14) for rs12979860 and 10.08 (2.98–18.59) for rs12980275. Figure 2b show that patients with chronic HCV infection the SVR rate of IL-28B rs8099917 TT was (25/27, 92.41%), IL-28B rs12979860 CC was (26/28, 92.86%) and IL-28B rs12980275 AA was (24/27, 88.89%). In contrast, only 7.41, 7.14 and 11.11% reached SVR with IL-28B SNP rs8099917 TG + GG, rs12979860 CT + TT, and rs12980275 AG + GG, respectively. Patients with protective genotypes were more likely to obtain SVR.

Table 3 IL-28B gene polymorphism in patients with chronic HCV infection and clinical characteristics of patients with different IL-28B SNPs

Genotype	SNP	Percent (%)	Age (y)	Sex (No. of Patients, %)		Viral Load (10^6 IU/mL), range	ALT (U/L), range	AST (U/L), range
				Male	Female			
IL-28B rs8099917	TT (n = 39)	76.47	48 (25–64)	54 (52.9)	52 (47.1)	7.98 (0.24–72.46)	34 (18–179)	38 (17–203)
	TG + GG (n = 12)	23.43	47 (22–58)	21 (55.3)	16 (44.7)	9.25 (0.89–59.71)	36 (28–150)	40 (24–138)
IL-28B rs12979860	CC (n = 39)	76.47	49 (22–64)	57 (52.3)	52 (47.7)	10.23 (1.02–68.52)	35 (21–112)	32 (19–143)
	CT + TT (n = 12)	23.43	49 (20–58)	18 (52.9)	16 (47.1)	8.72 (0.48–65.32)	37 (19–135)	34 (17–178)
IL-28B rs12980275	AA (n = 37)	72.55	47 (28–64)	51 (51.5)	48 (48.5)	11.25 (1.37–66.68)	38 (22–144)	31 (20–123)
	AG + GG (n = 14)	27.45	46 (25–59)	24 (54.5)	20 (45.5)	9.67 (0.69–71.26)	32 (19–179)	29 (17–112)
			Z = 0.125	chi-squared = 0.413		Z = 0.579	Z = 0.378	Z = 2.143
P value			.912	.648		.825	.617	.346



Role of IL-28B SNP and HCV genotype in antiviral efficacy
 We combined the results of IL-28B SNP and HCV genotype and analyzed the correlation between these factors. We found that 12/51 patients with HCV genotype 1b infection obtained SVR, in which 8/12 cases were rs12979860 CC (shown in Fig. 2c). We also found that the 7 of 10 patients infected with HCV genotype 2a who obtained SVR were rs12979860 CC. In addition, 2 in 17 patients with HCV genotype 1b infection and SNP rs12979860 CC did not obtain SVR, and only 1/3 patients with HCV genotype 2a infection and SNP rs12979860 CC did not obtain SVR. Patients HCV genotype 2a infection with IL-28B SNP rs12979860 CC were more likely to reach SVR.

Association of liver fibrosis staging and cirrhosis in patients with chronic HCV infection and antiviral efficacy
 Because there were only 190 out of 231 patients did PLT detection, and APRI and FIB-4 were calculated according to results of patients' PLT. So APRI score and FIB-4 index were calculated in 190 of 231 patients with chronic HCV infection. Sixty patients had FIB-4 index > 3.25, including 32 patients with genotype 1b infection

and 21 patients with genotype 2a infection. In this patient group, 31.0% of patients with HCV genotype 1b (19/32 × 58/111) and 39.4% of patients with genotype 2a (11/21 × 67/89) reached SVR (not statistically significant; $P > 0.05$). Thirty-nine patients had APRI score > 2, including 11 patients with genotype 1b and 8 patients with genotype 2a infection. In this patient group, 30.3% with HCV genotype 1b (11/19 × 58/111) and 50.2% with genotype 2a (8/12 × 67/89) reached SVR ($P < 0.05$). Although we could not prove that genotype affected the ability to reach SVR in patients with cirrhosis (APRI > 2), we did observe that APRI score > 2 significantly affected SVR. Details are shown in Tables 4 and 5.

Table 4 Characteristics of patients

Variables	No. of Patients (%of Total)
Total number of patients	231
Age ± standard deviation, y	46.71 ± 14.34
Male	113
Female	118
APRI data	190 (82.3)
FIB-4 data	190 (82.3)

Table 5 FIB-4 index, APRI scores and SVR of patients

Genotype	No. of Patients (% of Total)	No. of Patients with FIB-4 > 3.25 (% of Total)	No. of Patients with APRI > 2 (% of Total)	Total SVR (%)	No. of Patients with FIB-4 > 3.25 and SVR (%)	No. of Patients with APRI > 2 and SVR (%)
1b	90 (81.1)	32 (16.8)	19 (10.0)	58 (64.4)	19 (31.0)	11 (30.3)
2a	76 (85.4)	21 (11.1)	12 (6.3) [*]	67 (88.1)	11 (39.4)	8 (50.2)
Other	24 (77.4)	7 (3.7)	8 (4.2)	13		
Total	190 (82.3)	60 (31.6)	30 (20.5)	138 (72.6)		

^{*} $P < 0.05$

Discussion

China has shown a new trend in HCV infection, with epidemic levels of genotypes 1, 2, 3 and 6 and no genotypes 4 or 5 found. The most common genotype in China is 1b and 2a, with incidence rates of 73.1 and 18.5%, followed by genotypes 3a, 6a, 3b and 1a. Genotypes 3 and 6 are geographically distributed more widely [20]. In our group, which included 230 patients with chronic HCV infection, sequencing results showed that the incidence of HCV in the Shaanxi region was >86% with genotypes 1 and 2, with much lower numbers with genotypes 3 and 6, and none with genotype 4. More patients had genotype 1b (48.05%) and 2a (38.53%), followed by 1a, 3a, 3b, 2b and 6a. The high percent of genotype 2a might be one important reason for high SVR. And we truly found that patients with genotype 2a had greater SVR rates (75.28%) than patients with genotype 1b (52.25%). The results have a slight discrepancy versus the previous reports, which SVR rates for patients with genotype 1 were 42–46% and non-type 1 genotype were 76–82% [10, 21–23].

Furthermore, our SNP analysis results of 51 patients with chronic HCV infection (IL-28B rs8099917, IL-28B rs12979860 and IL-28B rs12980275 SNP) and sequencing results of 230 patients with chronic HCV infection showed that more patients had IL-28B rs8099917 TT versus rs8099917 GG, more had IL-28B rs12979860 CC versus TT, and more had IL-28B rs12980275 AA versus GG in Northwest China, similar to some previous reports [24, 25]. Presence of rs8099917 is one of the independent predictors in HCV 1b patients treated with PEG-IFN- α /R or interferon- α 2 only. Presence of rs12980275 has great relevance with SNP of rs12979860 [26], which plays an important role in the prediction of SVR in HCV patients treated with PEG-IFN- α /R, particularly in patients with HCV genotype 1 or 4 [10, 27]. So rs8099917TT, rs12979860CC, and rs12980275AA were considered to be protective genotypes [28]. In this study, SVR rates of patients with IL-28B rs8099917 TT, rs12979860 CC and rs12980275 AA were 92.41% (25/27), 92.86% (26/28) and 88.89% (24/27) separately. SVR rates in patients with protective genotypes accounted for more than sixty percent of total, whereas the SVR rates of non-protective

genotypes were very low. This suggested that the protective IL-28B genotypes were more likely to result in patients with chronic HCV infection obtaining SVR, which is consistent with previous reports [26–29]. In addition, we corrected for age, sex, AST and ALT levels, HCV genotype and other factors with the use of SNPStats software [30] and found that patients with chronic HCV infection who obtained SVR 24 weeks after standard of care antiviral treatment were closely related to HCV genotype and IL-28B SNP ($P < 0.05$). That means more than sixty percent of patients are suitable for PEG-IFN- α /R treatment. Well, the major limitation in this part of study is that the sample amount was relatively too small to determine the role of IL-28B gene polymorphism in antiviral efficacy. However, our findings were in accordance with previous data [26–29].

Interestingly, we found that differences in cirrhosis progression between 1b and 2a were statistically significant, confirming that HCV genotype can influence the progression of liver cirrhosis. FIB-4 index > 3.25 or APRI score > 2 indicated that patients had significant liver fibrosis or even cirrhosis [31]. In this study, the SVR rates of patients with FIB-4 index > 3.25 and genotypes 1b and 2a were 31.0 and 39.4%, respectively, which were much lower than that shown in patients with genotype 1b (62.06%) and genotype 2a (74.54%) with FIB-4 index \leq 3.25. This indicated that patients with obvious liver fibrosis were less likely to reach SVR, which was associated with HCV genotype (1b or 2a). In addition, SVR rates of patients with APRI score > 2 were 30.3% for genotype 1b and 50.2% for genotype 2a. The large difference indicated that patients with cirrhosis had greater difficulty reaching SVR, for both HCV genotype 1b and 2a, and the progression of cirrhosis (APRI > 2) could be influenced by genotype. The clearance of HCV in patients with advanced-stage liver fibrosis can reduce the incidence of decompensated liver cirrhosis.

Conclusions

There were high proportion of HCV genotype 1b and 2a in Northwest China. In both HCV 1b and 2a genotypes, patients with protective-genotype of IL-28B

were more likely to obtain SVR. However, those with significant fibrosis or cirrhosis were less likely, no matter their genotype. Combined factors of HCV genotype, IL-28B genotype, FIB-4 and ARPI potentially have a very high prediction and clinical value regarding treatment with PEG-IFN- α /R and prognostic evaluation of chronic hepatitis C patients.

Abbreviations

APRI: Aspartate aminotransferase-to-platelet ratio index; CHC: Chronic hepatitis C; FIB-4: Fibrosis 4 index; HCV: Hepatitis C virus; IL-28B: Interleukin (IL)-28B; PEG-IFN- α /R: Pegylated interferon-alpha combined with ribavirin; SNP: Single-nucleotide polymorphisms; SVR: Sustained viral response

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Authors' contributions

YL and JW performed experiments, analyzed the data, designed the Figures and drafted the manuscript. YX and LY contributed to experiments and helped data analysis. JW and HL were also involved in performing experiments. BX assisted with analyzing and interpreting data, and provided technical support. XH and YM designed the research, analyzed the data and critical revision of manuscript for important intellectual content. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Clinical Laboratory Medicine, Xijing Hospital, The Fourth Military Medical University, 169 Changle West Road, Xi'an, Shaanxi 710032, People's Republic of China. ²Department of Infectious Disease, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi 710032, People's Republic of China. ³Pharmacy Department, Tangdu Hospital, The Fourth Military Medical University, Xi'an, Shaanxi 710038, People's Republic of China. ⁴Shandong International Trust Co., Ltd, Jinan, Shandong 250013, People's Republic of China.

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