Assessment of health-related quality of life predicts the outcome of pegylated interferon and ribavirin therapy for chronic hepatitis C

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Short title: HRQOL and PegIFN for HCV

List of abbreviations:

HCV, hepatitis C virus; IFN, interferon-α; PegIFN, pegylated IFN-α; RBV, ribavirin; SVR, sustained virological response; HRQOL, health-related quality of life; SNP, single-nucleotide polymorphism; SF-36, 36-item short-form health survey; MCS, mental component score; PCS, physical component score.

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ABSTRACT

Background: Chronic infection with hepatitis C virus (HCV) decreases health-related quality of life (HRQOL). The present study was planned to investigate the impact of HRQOL of patients with chronic hepatitis C (CHC) on the outcomes of therapy with pegylated interferon and ribavirin, in addition to IL28B polymorphisms.

Methods: The present study enrolled 228 CHC patients, and assessed their HRQOLs prospectively with the 36-item short-form health survey.

Results: The patients with chronic hepatitis C have lower physical HRQOL status than the general population (*P* = 0.037, the *Z* test). The patients with advanced liver diseases exhibited further decreases in HRQOL (*P* = 0.036, Spearman's rank correlation coefficient). The score of total HRQOL was significantly lower in the group with sustained virological response (SVR) to the therapy with pegylated interferon and ribavirin than the non-SVR group (P = 0.031, the Mann-Whitney U test), with significantly lower scores of mental component and its comprising subscales in the SVR group. Stepwise multivariate logistic regression analysis showed that low HRQOL score ≤400 points was significantly associated with SVR (odds ratio = 2.4, *P* = 0.013), independently from high platelet counts, low HCV RNA, favorable SNP type of IL28B, and HCV serotype 2. The patients with low HRQOL

score will had significantly less decrease in HRQOL score by 4 weeks of the treatment than those with high HRQOL score at baseline (P = 0.0045).

Conclusions: HRQOL is one of the significant predictor of the outcomes of therapy with pegylated interferon and ribavirin independently from IL28B polymorphism.

Key words: Interferon, QOL, and HCV

INTRODUCTION

More than 170 million people worldwide are infected with hepatitis C virus (HCV) infection, which causes chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma [1, 2]. The combination with pegylated Interferon-α (PegIFN) and ribavirin (RBV) is widely used for the treatment of patients with chronic hepatitis C [3]. Recent therapeutic regimens using directly acting antiviral agents with PegIFN and RBV have improved sustained virological response (SVR) rate up to 80% for the patients with HCV genotype 1 [4-6].

The health-related quality of life (HRQOL) has been studied in patients with various diseases, such as gastrointestinal disorders, diabetes mellitus, heart disease and depression, and is profoundly associated with disease severity and progression [7-11]. In terms of HCV, chronic viral infection itself decreases the HRQOL of the patients [12], and the HRQOL may affect the outcome of interferon therapy [13-20]. However, the impact of HRQOL has not been well understood in comparison with other predictive factors such as the single-nucleotide polymorphism (SNP) of IL28B or HCV serogroup.

The present study evaluated the HRQOL of the patients with chronic hepatitis C prospectively before and during the combinations of PegIFN and RBV, in order to clarify the impact of HRQOL on the outcomes of IFN therapy. Our results indicated that total HRQOL before the therapy is significantly associated with sustained viral response for the patients

with chronic hepatitis C, independently of the SNP types of IL28B and HCV serogroup.

METHODS

Patients

The present study enrolled the patients with chronic HCV infection, of whom the HRQOLs were evaluated at Okayama University hospital between 2006 and 2011. Patients co-infected with hepatitis B virus or human immunodeficiency virus, and patients with complicating autoimmune liver diseases were not included in the study. Hepatocellular carcinoma was ruled out by means of dynamic computed tomography or magnetic resonance imaging, combined with measurement of the serum levels of alpha-fetoprotein, and des-γ-carboxy prothrombin. The study was performed in accordance with the Helsinki Declaration, and all the protocols were approved by the ethics committees of the institute. All patients provided informed consent before enrollment into the study. This study was registered for University Hospital Medical Information Network‐Clinical Trials Registry (UMIN 000001031).

Interferon therapy

The patients received a combination of PegIFN-α2a (180 μg) or PegIFN-α2b (1.5 μg/kg of

body weight) by subcutaneous injection every week with RBV (600–1000 mg daily, according to body weight). The doses of PegIFN and RBV were individually reduced during the treatment whenever needed to lessen adverse effects, and these dose reductions were performed according to the labeling.

Measurement of health-related quality of life

All the patients were evaluated to determine their HRQOL score before the treatment, by using the 36-item short-form health survey (SF-36) version 2nd [21-23]. One hundred and seventy-six patients were longitudinally evaluated for changes of HRQOL score. Their HRQOL scores were assessed before the treatment, at 4 weeks of treatment, at the end of treatment, and at 24 weeks after treatment. The SF-36 consists of 8 subscales (physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional, and mental health), with each subscale having been adjusted so that a score of 50 corresponds to the mean value for that subscale in the general population. The general population in the SF-36 for Japanese is established based on the data of 6053 healthy Japanese residents with 20 to 80 years of age [23]. The mean scores of total HRQOL of the general population were quoted as 400 points. The scores of physical, mental, and role-social components were also estimated according to the proposal for the general

population in the previous report [23].

Diagnosis of liver histology

Liver fibrosis stage and hepatitis activity grade were assigned for all the patients by two pathologists according to the criteria of Desmet et al. [24].

Genotyping of single nucleotide polymorphism

Genomic DNA was extracted from whole-blood samples by means of a QIAamp DNA Mini Kit according to the manufacturer's protocol (Qiagen, Tokyo, Japan). The SNP rs 8099917 of IL28B was genotyped using the TaqMan predesigned SNP genotyping assays, as recommended by the manufacturer (Applied Biosystems, Tokyo, Japan). The SNP genotypes of all the samples assessed could be obtained with this system.

Statistical analysis

Data are expressed as the mean ± standard deviation. Differences in HRQOL scores between groups were compared by using the Mann-Whitney U test or Spearman's rank correlation coefficient. The ratios of patients attaining SVR were compared between the groups with the Fisher exact probability test. Stepwise multivariate logistic regression

analysis was utilized to estimate the effects of patient characteristics on SVR and the associations of patient characteristics with the HRQOL scores. In the logistic regression analysis of the factors related to the therapeutic outcomes of PegIFN and ribavirin therapy, the cut-offs of the factors were determined by evaluating the efficacy with the receiver operating characteristic area curve. A value of P <0.05 was considered significant. Statistical analysis was performed with JMP software (SAS Institute, Cary, NC).

Results

The patient characteristics associated with HRQOL

The present study enrolled 228 patients (114 male and 114 female) with a mean age of 56 ± 11 years. The patient characteristics are shown in Table 1. Of those patients, 152 patients had HCV serotype 1, and 76 had serotype 2. The genotype of the SNPs rs 8099917 of IL28B were TT in 164 patients (74%) and TG or GG in 59 patients (26%). In terms of HRQOL, physical component, and its comprising subscales of role-physical and general health were significantly lower among the patients than the general population (P = 0.037, 0.002, <0.001, respectively, the Z test), while the HRQOL scores of mental and role-social components showed similar scores to the general population. Associations of patient

characteristics were evaluated with the HRQOL, as shown in Figure 1. Patients with high age tended lower score of physical component, and higher score of mental component than those with young age (r = -0.20, *P* = 0.0034, and r = 0.17, *P* = 0.011, respectively, Spearman's rank correlation coefficient). Low platelet counts were also associated with low scores of physical component (r = 0.14, *P* = 0.036). Mental component differed significantly by the SNP types of IL28B (*P* = 0.036, the Mann-Whitney U test). Gender, HCV serotype, and the levels of alanine aminotransferase, and γ-glutamyl transpeptidase did not affect the levels of the HRQOL.

Significant impact of HRQOL on the outcome of interferon therapy

The HRQOL scores among the SVR group were significantly lower than those among the group of transient virological response (389 ± 64, and 414 ± 50, respectively, *P* = 0.027, the Mann-Whitney U test). The group of transient virological response did not differ in the HRQOL scores significantly from the group of null or partial virological response (402 ± 61, *P* = 0.42). Therefore, the HRQOL score was compared between the SVR and non-SVR groups (Table 2). The score of total HRQOL was significantly lower in the SVR group than the non-SVR group (*P* = 0.031), which reflected significantly lower scores of mental component and its comprising subscales in the SVR group than the non-SVR group. The

impact of HRQOL on SVR was also assessed in the logistic regression analysis, and HRQOL score was inversely correlated to SVR (P = 0.028). The cut-off of the HRQOL score was determined with the receiver operator characteristic curve, and a cut-off of 400 points gave the best sensitivity and specificity (52% and 70%, respectively). Therefore a cut-off of 400 points, which was the mean scores of total HRQOL of the general population, was used in further logistic regression analysis. The ratio of the patients attaining a SVR was significantly higher among the patients with the HRQOL scores <400 points than those with HRQOL scores ≥400 points (72% and 52%, P = 0.0038, the Fisher exact probability test). Similarly, significant differences in the SVR rate were obtained among the patients with HCV serotype 1 and those with HCV serotype 2 (62% vs. 45%, P = 0.048, and 91% vs. 67%, P = 0.025, respectively). As shown in Table 3, stepwise multivariate logistic regression analysis by using the patient characteristics including HRQOL score showed that low HRQOL score ≤400 points was significantly associated with SVR (odds ratio = 2.4, P = 0.013), independently from high platelet counts, low HCV RNA, favorable SNP type of IL28B, and HCV serotype 2. When the 3 components of HRQOL were used for the analysis instead, mental component score (MCS) was also selected as the significant predictor of SVR (odds ratio = 2.4, P = 0.0048). The receiver operating characteristic area curves, constructed from the results of the multivariate logistic regression analysis, showed the area under the curve

was 0.81 with total HRQOL score, while 0.80 with MCS, showing superior applicability of total HRQOL score to MCS. In addition, subgroup analysis for the patients with HCV serotype 1 was done. The cut-off of the HRQOL score was determined as 415 points with the receiver operator characteristic curve. Stepwise multivariate logistic regression analysis showed that low HRQOL score ≤415 points was significantly associated with SVR (odds ratio = 2.3, *P* = 0.039), independently from low levels of γ-glutamyl transpeptidase, high platelet counts, and favorable SNP type of IL28B (Table 4). The adherence of PegIFN and ribavirin did not differ between the patients with high and low HRQOL scores prior the treatment; greater than 80% of the scheduled dose of PegIFN was received by 63% of the patients with high HRQOL score, and by 72% of the patients with low HRQOL score (*P* = 0.28, the Fisher exact probability test), while greater than 80% of the scheduled dose of ribavirin was received by 61% of the patients with high HRQOL score and 66% of the patients with low HRQOL score (*P* = 0.57). The incidence of treatment discontinuation did not differ between the patients with high and low HRQOL scores prior the treatment; 19.1% of the patients with high HRQOL score, and 14.4% of the patients with low HRQOL score (*P* = 0.38, the Fisher exact probability test).

Changes of HRQOL during IFN therapy

One hundred and seventy-six patients were longitudinally evaluated for changes of HRQOL score. The total scores and the scores of all the three components were decreased in most patients by 4 weeks of treatment, and the decreased scores were maintained until the end of treatment. The decreases during 4 weeks of the treatment did not differ significantly between the SVR and non-SVR groups (P = 0.22, 0.11, and 0.20 and 0.87, respectively, the Mann-Whitney U test, Figure 2). No significant difference in the decreases between the start and the end of treatment was observed between the two groups. At 24 weeks after the treatment, the patients in the SVR group showed higher total score and MCS compared to baseline, while the HRQOL scores of the patients in the non-SVR group did not improved to the baseline (P <0.001, and <0.001, respectively). As shown in Figure 3, the patients with low HRQOL scores had significantly less decrease of HRQOL during 4 weeks of the treatment than those with high scores (P = 0.0045), which might reflect the significant decreases in physical component score (PCS) and MCS (P = 0.013, and 0.014, respectively).

Discussion

The present study investigated the HRQOL of the patients with chronic hepatitis C in physical, mental and social aspects before and during the treatment prospectively, and

evaluated the impact of HRQOL as the predictive factors of interferon therapy. The present study is the first to clarify that a low HRQOL before treatment is significantly associated with SVR to PegIFN therapy and that HRQOL score before treatment is significantly associated with changes of HRQOL score during early phase of treatment. It should be noted that the HRQOL predict therapeutic outcome independently from HCV serotype, the SNP genotype of IL28B, and platelet counts.

SF-36, the measurement of HRQOL in the present study, is utilized worldwide as a survey for HRQOL. It can evaluate HRQOL status precisely using 3 components and 8 subscales. The resulting HRQOL scores can be compared with the standard scores generalized by general population. In the present study, HRQOL scores of the patients with chronic hepatitis C were significantly lower than those of the general population in 2 of 8 subscales, indicating that chronic hepatitis C decreases physical aspects of HRQOL. Patients with advanced liver diseases exhibit further decreases in HRQOL, reflecting severe fatigue from a physical point of view. These results are similar to the previous reports on HRQOL in patients with chronic hepatitis C [16, 17].

The present study revealed that HRQOL before treatment is significantly associated with attaining a SVR to PegIFN therapy for the patients with chronic hepatitis C. Further analysis indicated that there are significant differences in the scores of the MCS before treatment

between the SVR and non-SVR patients, but not of the PCS or role-social component score. These results are consistent with the previous reports on depression during PegIFN therapy in different modes of assessments, demonstrating that IFN-induced depression-specific symptoms are distinct from general somatic and fatigue symptoms [13, 14], and that minimally depressed patients are less likely than mildly and moderately depressed patients to attain an antiviral treatment response by evaluating the degree of depression with Beck Depression Inventory [15].

In order to clarify the mechanisms how low HRQOL may contribute to high possibility of attaining a SVR, we investigated patient characters in the associations with low HRQOL. The patients with favorable SNP of IL28B had significantly lower HRQOL score than those with unfavorable SNPs. However, low HRQOL score significantly associated with SVR independently from favorable SNP of IL28B with multivariate regression analysis. Therefore our results may indicate that HRQOL itself is an independent predictor for the outcome of interferon therapy. The association of drug adherence of PegIFN and ribavirin or incidence of treatment discontinuation with low HRQOL at baseline was not obvious in the present study.

Interestingly there were significant associations between the HRQOL score at baseline and the changes of HRQOL score during early phase of treatment; the patients with low

HRQOL score will have significantly less decrease in HRQOL score by 4 weeks of the treatment than those with high HRQOL score at baseline. The patients with low HRQOL score at baseline may tolerate the changes of physical and mental condition with the treatment and maintain the HRQOL during the treatment, while the vulnerability to aggravating condition during the treatment may be observed in those with high HRQOL score. The unfavorable influence of severely decreased HRQOL during IFN treatment are consistent with the previous report showing that severe fatigue during the treatment may inversely affect therapeutic outcomes [19]. The reason why less decrease in HRQOL score was not significantly associated with SVR was not obvious in the present study.

In conclusion, patients with chronic hepatitis C have lower HRQOL status than the general population. Advanced liver diseases may further worsen HRQOL. HRQOL status before treatment is one of the significant factors to predict therapeutic outcomes of PegIFN therapy independently from HCV serotype, the SNP genotype of IL28B, and platelet counts.

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The authors declare that no conflicts of interest exist.

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Table 1: Patient characteristics of the patients enrolled in the study

Patient characters		HRQOL scales	
Age (years)	56 ± 11‡	Total HRQOL	396 ± 62‡
Gender (male/female)	114/114	Physical component	49 ± 9‡
ALT (IU/L)	67 ± 54‡	Mental component	51 ± 9‡
γGTP (IU/L)	55 ± 56‡	Role-social component	49 ± 12‡
Platelet count (10000 /mm^3)	18 ± 6‡	Physical function	50 ± 10‡
HCV serogroup (1/2)	152/76	Role-physical	47 ± 12‡
HCV RNA (log IU/ml)	6.0 ± 0.9‡	Bodily pain	54 ± 10‡
rs 8099917 (TT/TG or GG/NA)	164/59/5	General health	46 ± 10‡
Liver fibrosis (stage 1-2/3-4/NA)	127/55/46	Vitality	51 ± 10‡
Therapeutic outcome (SVR/TVR/NVR)	138/40/50	Social function	49 ± 11‡

	Role-emotional	49 ± 10‡
	Mental health	51 ± 9‡

‡: Mean ± standard deviation.

HCV, hepatitis C virus; ALT, alanine aminotransferase; γGTP, γ-glutamyl transpeptidase; NA, not assessed; SVR, sustained virological response; TVR, transient virological response; NVR, null or partial virological response; HRQOL, health related quality of life.

Table 2: The HRQOL score and its associations with sustained virological response

HRQOL scale	SVR (N = 138)	Non-SVR (N = 90)	*P*
Total score	389 ± 64‡	408 ± 56‡	0.031
Physical component	49 ± 10‡	49 ± 10‡	0.52
Mental component	50 ± 9‡	54 ± 9‡	＜0.001
Role-social component	49 ± 12‡	49 ± 12‡	0.69
Physical function	49 ± 11‡	50 ± 10‡	0.73
Role-physical	47 ± 13‡	48 ± 11‡	0.47
Bodily pain	53 ± 10‡	54 ± 9‡	0.91
General health	45 ± 10‡	48 ± 9‡	0.020
Vitality	49 ± 10‡	54 ± 9‡	＜0.001
Social function	48 ± 11‡	50 ± 11‡	0.0059
Role-emotional	49 ± 10‡	50 ± 10‡	0.075
Mental health	50 ± 9‡	53 ± 8‡	0.013

‡: Mean ± standard deviation.

HRQOL, health related quality of life; SVR, sustained virological response.

Table 3: Logistic regression analysis of the factors related to the therapeutic outcomes of PegIFN and ribavirin therapy.

	Univariate analysis		Multivariate analysis	
Factors	Odds ratio (Range†)	*P*	Odds ratio (Range†)	*P*
Age (>65 years)	0.55 (0.29-1.0)	0.057	0.64 (0.29-1.4)	0.27
Gender (male)	1.6 (0.91-2.7)	0.10		
ALT (>80 IU/L)	0.73 (0.40-1.3)	0.32		
γGT (>70 IU/L)	0.43 (0.23-0.81)	0.0082	0.49 (0.24-1.0)	0.062
Platelet count (>150000 /mm^3)	2.5 (1.4-4.3)	0.0015	3.5 (1.8-7.1)	<0.001
HCV RNA (>5 Log IU/ml)	0.34 (0.12-0.95)	0.039	0.23 (0.061-0.85)	0.027
HCV serotype (Serotype 2)	3.2 (1.7-6.0)	<0.001	2.9 (1.4-6.0)	0.0053
SNP rs 8099917	5.5 (2.9-11)	<0.001	8.8 (3.9-20)	<0.001

(TT = 1)				
Total HRQOL score				
	0.43 (0.25-0.75)	0.0031	0.43 (0.22-0.83)	0.013
(>400 points)				

†: 95% confidence interval.

ALT, alanine aminotransferase; γGT, γ-glutamyl transpeptidase; HCV, hepatitis C virus; HRQOL, health related quality of life.

Table 4: Logistic regression analysis of the factors related to the therapeutic outcomes of PegIFN and ribavirin therapy for the patients with HCV serotype 1.

	Univariate analysis		Multivariate analysis	
Factors	Odds ratio (Range†)	*P*	Odds ratio (Range†)	*P*
Age (>65 years)	0.42 (0.19-0.92)	0.030	0.53 (0.19-1.4)	0.21
Gender (male)	1.8 (0.93-3.4)	0.084		
ALT (>80 IU/L)	0.57 (0.26-1.2)	0.16		
γGT (>70 IU/L)	0.38 (0.18-0.81)	0.013	0.36 (0.14-0.89)	0.027
Platelet count (>150000 /mm^3)	2.5 (1.3-4.8)	0.0071	4.6 (2.0-11)	<0.001
HCV RNA (>5 Log IU/ml)	0.33 (0.087-1.3)	0.11		
SNP rs 8099917 (TT = 1)	7.4 (3.1-17)	<0.001	10 (3.7-28)	<0.001
Total HRQOL score	0.45 (0.27-1.3)	0.016	0.44 (0.20-0.96)	0.039

(>415 points)

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†: 95% confidence interval.

ALT, alanine aminotransferase; γGT, γ-glutamyl transpeptidase; HCV, hepatitis C virus; HRQOL, health related quality of life.

Figure legends

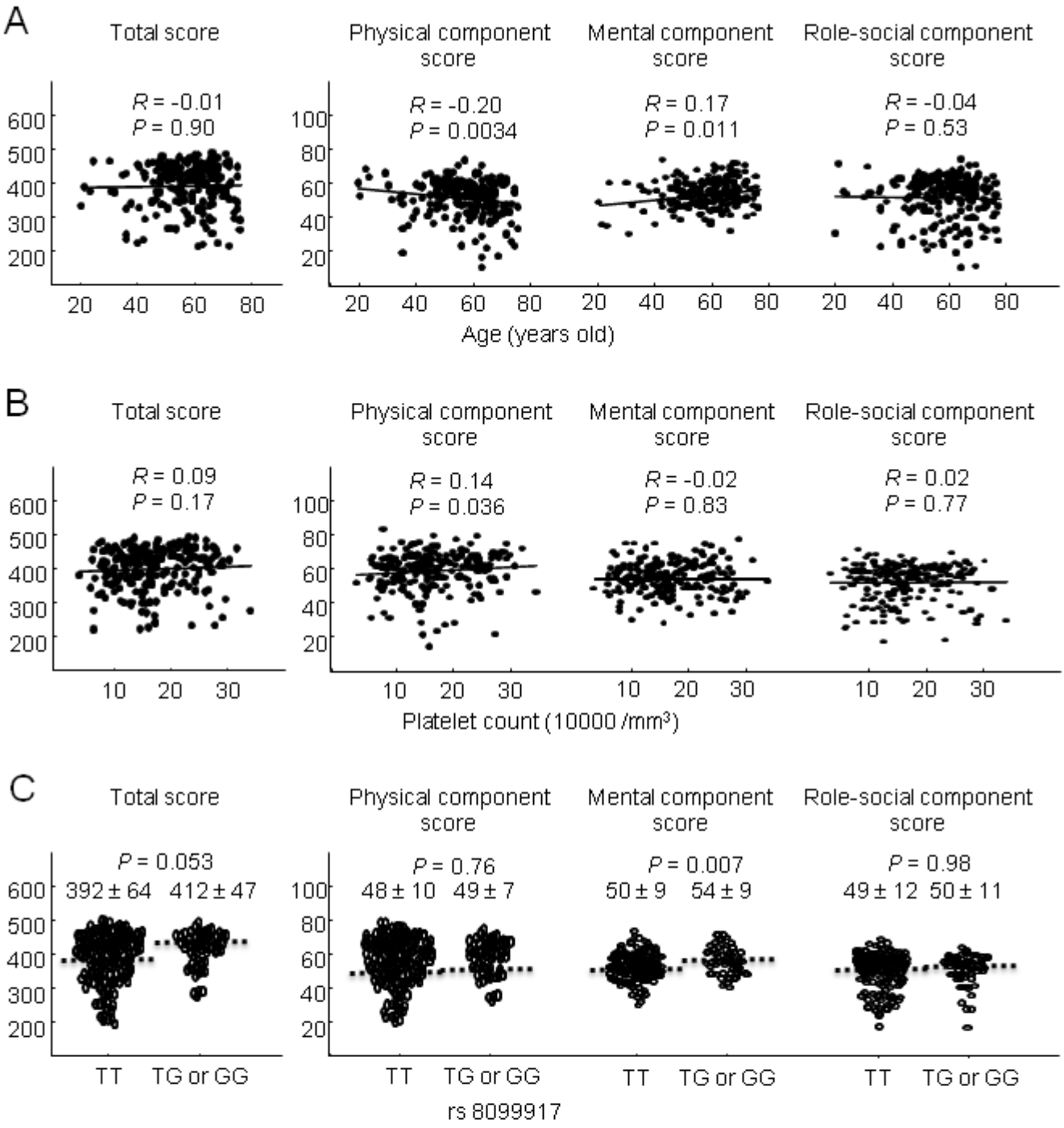
Figure 1: The patient characteristics associated with HRQOL.

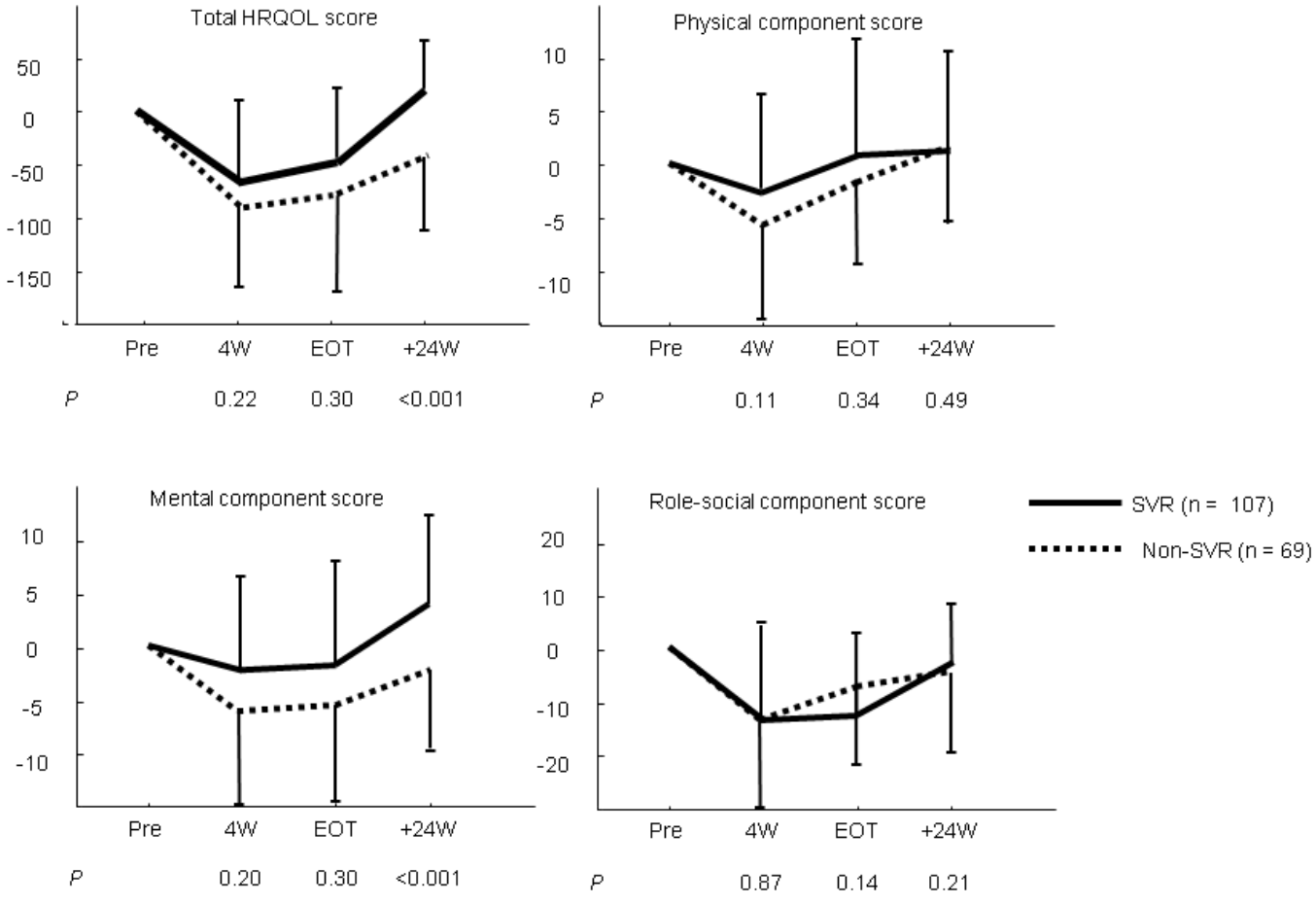
The HRQOL scores of the patients were plotted by the total score, and the scores of physical, mental, and role-social component. The associations of age (Figure 1A) and platelet counts (Figure 1B) with HRQOL score were evaluated by Spearman's rank correlation coefficient. The difference of HRQOL score were compared for each patient group classified by the genotype of rs 8099917 of IL28B by the Mann-Whitney U test in Figure 1C.

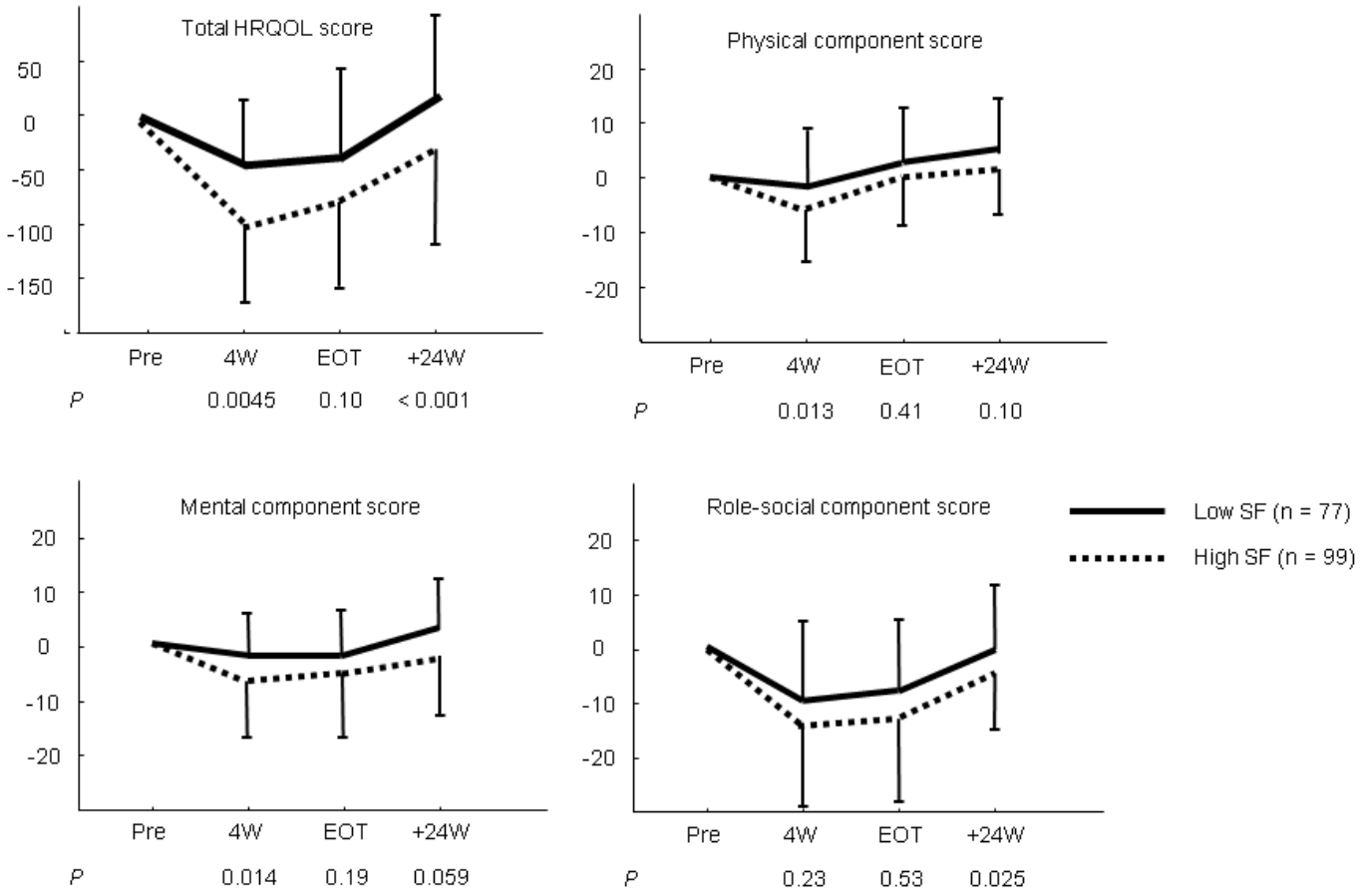
Figure 2: The changes of HRQOL score during the treatment.

One hundred and seventy-six patients were longitudinally evaluated for the changes of HRQOL during interferon therapy. Their HRQOL scores were assessed before the treatment (Pre), at 4 weeks of treatment (4W), at the end of treatment (EOT), and at 24 weeks after treatment (+24W). Figure 2A shows the mean change of the HRQOL scores of the group attaining a sustained virological response (SVR) with the bold line (n = 107), while the mean change in HRQOL for the non-SVR group with the dotted line (n = 69). Figure 2B shows the mean change of the HRQOL scores of the group with the baseline of HRQOL

≤400 points with the bold line (n = 77), while the mean change in HRQOL for the group with the baseline of HRQOL >400 points with the dotted line (n = 99).


A
Total score
Physical component score
Mental component score
Role-social component score
R = -0.01
P = 0.90
R = -0.20
P = 0.0034
R = 0.17
P = 0.011
R = -0.04
P = 0.53
600
500
400
300
200
100
80
60
40
20
20 40 60 80
Age (years old)
B
Total score
Physical component score
Mental component score
Role-social component score
R = 0.09
P = 0.17
R = 0.14
P = 0.036
R = -0.02
P = 0.83
R = 0.02
P = 0.77
10 20 30
Platelet count (10000 /mm3)
C
Total score
Physical component score
Mental component score
Role-social component score
P = 0.053
392 ± 64 412 ± 47
P = 0.76
48 ± 10 49 ± 7
P = 0.007
50 ± 9 54 ± 9
P = 0.98
49 ± 12 50 ± 11
TT TG or GG
rs 8099917


Total HRQOL score
50
0
-50
-100
-150
Pre
4W
EOT
+24W
P
0.22
0.30
<0.001
Physical component score
10
5
0
-5
-10
Pre
4W
EOT
+24W
P
0.11
0.34
0.49
Mental component score
10
5
0
-5
-10
Pre
4W
EOT
+24W
P
0.20
0.30
<0.001
Role-social component score
20
10
0
-10
-20
Pre
4W
EOT
+24W
P
0.87
0.14
0.21
SVR (n = 107)
Non-SVR (n = 69)


Total HRQOL score
50
0
-50
-100
-150
Pre
4W
EOT
+24W
P
0.0045
0.10
< 0.001
Physical component score
20
10
0
-10
-20
Pre
4W
EOT
+24W
P
0.013
0.41
0.10
Mental component score
20
10
0
-10
-20
Pre
4W
EOT
+24W
P
0.014
0.19
0.059
Role-social component score
20
10
0
-10
-20
Pre
4W
EOT
+24W
P
0.23
0.53
0.025
Low SF (n = 77)
High SF (n = 99)