Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5102-20
Intern Med 59: 2653-2660, 2020
http://internmed.jp

【 ORIGINAL ARTICLE 】

Direct-acting Antivirals Improved the Quality of Life, Ameliorated Disease-related Symptoms, and Augmented Muscle Volume Three Years Later in Patients with Hepatitis C Virus

Tatsuki Ichikawa[1,2], Hisamitsu Miyaaki[3], Satoshi Miuma[3], Yasuhide Motoyoshi[1], Mio Yamashima[1], Shinobu Yamamichi[1], Makiko Koike[2], Yusuke Nakano[2], Tetsurou Honda[1], Hiroyuki Yajima[1], Ryouhei Uehara[1], Osamu Miyazaki[1], Yasutaka Kuribayashi[1], Keiji Kira[3], Naota Taura[3] and Kazuhiko Nakao[3]

Abstract:

Objective Patient-reported outcomes (PROs) are important measures of the quality of life (QOL) and symptoms in patients with hepatitis C virus (HCV). We evaluated the PROs at the beginning of direct-acting antiviral (DAA) treatment and three years later. A low QOL in patients with chronic liver disease suggested a low muscle mass. We compared the relationship between the QOL and muscle mass.

Methods DAAs were administered to 100 patients with HCV infection. The PROs included the cirrhosis-related symptom score (CSS), presence of restless legs syndrome, Pittsburg sleep quality index (PSQI) to evaluate sleep disturbance, SF-36 to measure the QOL, and calculated body muscle mass (CBMM) measured at the beginning of treatment and three years later. Computed tomography (CT) was used to screen 82 patients for hepatocellular carcinoma at the beginning of treatment and three years later. Cross-sectional CT images of the third lumbar vertebrae were analyzed to evaluate the body composition.

Results The general health perception (GHN) of SF-36 was better at three years after DAA administration than at the beginning. Changes in the GHN (dGHN) were related to an improved sleep quality on the PSQI and CSS and increased CBMM. The dGHN was positively related to changes in the skeletal muscle. The sleep quality, sleep latency, fatigue, and abdominal fullness were related to dGHN.

Conclusion The QOL is related to sleep disturbance and several other symptoms. Furthermore, in patients with an increased muscle volume after DAA treatment, increased muscle mass is associated with an improvement in the QOL.

Key words: direct-acting antiviral, disease-related symptom, hepatitis C virus, quality of life, skeletal muscle mass

(Intern Med 59: 2653-2660, 2020)
(DOI: 10.2169/internalmedicine.5102-20)

Introduction

Direct-acting antivirals (DAAs) have changed the treatment of hepatitis C virus (HCV) infection. DAA treatment has an extremely high sustained viral response (SVR) rate (96%) at 12 weeks after the end of treatment (1) and is associated with a reduced risk of mortality and hepatocellular carcinoma (HCC) (2). Therefore, DAA treatment should be considered in all patients with chronic HCV infection (2).

[1]Department of Gastroenterology, Nagasaki Harbor Medical Center, Japan, [2]Innovation and Translational Research Center, Nagasaki Harbor Medical Center, Japan and [3]Department of Gastroenterology and Hepatology, Graduate School of Biomedical Sciences, Nagasaki University, Japan

Received for publication April 16, 2020; Accepted for publication May 28, 2020

Correspondence to Dr. Tatsuki Ichikawa, ichikawa@nagasaki-u.ac.jp

However, due to the high price of DAAs, the value and affordability of HCV treatment are controversial. Recently, it was reported that DAA treatments were cost-saving, and measures to improve the quality of life (QOL) of patients after SVR are necessary to increase their cost-effectiveness (3-5). In real-world clinical settings, the symptom burden, medical comorbidities, and functional well-being of patients with chronic HCV infection after DAA therapy are unknown (6). Patient-reported outcomes (PROs) are important measures of the QOL and symptoms (7). Industry-sponsored registration trial results have reported improvements in the health-related QOL in patients with HCV infection after DAA treatment, but the extent to which these results are generalizable to the real-world setting is unknown (8). In addition, the PROs are typically assessed at baseline, during treatment, and 12 weeks after the end of treatment and are seldom evaluated in the long term (9).

We previously reported that HCV-related symptoms, but not the QOL, were improved by DAA treatment in 107 patients with SVR (9). The PROs measured at the start of treatment and one year later were the cirrhosis-related symptom score (CSS), presence of restless legs syndrome (RLS), Epworth sleepiness scale (ESS) and Pittsburg sleep quality index (PSQI) to evaluate sleep disturbance, Kessler 6 score (K-6) to evaluate psychological distress, and SF-36 to measure the QOL. The CSS, PSQI, K-6, and RLS scores improved one year after starting treatment. However, the QOL had not recovered. Therefore, in the present study, we evaluated the PROs at the beginning of DAA treatment and three years later.

Sarcopenia, low muscle mass, and low muscle strength are harmful symptoms observed in patients with liver disease and cirrhosis (10). A low QOL was reported by patients with chronic liver disease who had a low muscle mass (11). Furthermore, sarcopenia was associated with a poor QOL (12). In HCV-related liver disease, a low skeletal muscle (SM) mass was found to be related to advanced (13) and non-advanced (14) fibrosis, whereas in some patients with HCV infection, the muscle volume, which is associated with a low SM mass, increased after DAA (15). Recently, the sarcopenia index [SI; serum creatinine (Cr) / serum cystatin C (CysC) ×100] was reported as a fair measure of muscle mass in patients admitted to intensive-care units (16). In addition, a new body muscle mass [calculated body muscle mass (CBMM)] equation to estimate the total body muscle mass using Cr and CysC levels was developed (17). The difference in the Cr-based estimated glomerular filtration rate (GFR) and the CysC GFR (dGFR) has been reported as a marker of liver damage and muscle strength (18). We therefore compared PROs and the SI/CBMM/dGFR to evaluate the association between the QOL and muscle mass. In addition, when patients were screened for HCC using computed tomography (CT), the body composition was evaluated by CT, and each component of the body composition was compared with the QOL.

Materials and Methods

Patients

A series of 100 patients with chronic HCV infection were admitted to the Nagasaki Harbor Medical Center between October 2014 and January 2020. Patients were treated with DAAs, such as daclatasvir/asunaprevir (DCV/ASV; Bristol-Myers Squibb, Tokyo, Japan) or sofosbuvir/ledipasvir (SOF/LDV; Gilead Sciences, Tokyo, Japan) for 1b and sofosbuvir/ribavirin (SOF/RBV) for 2a/2b (RBV; Chugai Pharmaceutical, Tokyo, Japan). Combination DAA therapy was administered orally for 24 weeks in the case of DCV/ASV and for 12 weeks in the case of SOF/LDV and SOF/RBV. The SVR was determined at 24 weeks after the end of treatment. The SVR was achieved in all patients. Of the 100 patients, 69 had already been included in an antecedent report (9). This paper is a retrospective study.

Informed consent was obtained from each patient included in the study, and the patients were guaranteed the right to leave the study whenever they wished. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Nagasaki Harbor Medical Center.

PROs

The CSS questionnaire contains items regarding cirrhotic symptoms that include hand tremors, appetite loss, foot muscle cramps, fatigue, decreased strength, anxiety, abdominal fullness, abdominal pain, and a feeling of low energy (9). The ESS was used to evaluate daytime hypersomnolence (19). The sleep quality was evaluated using the Japanese version of the PSQI (20), which includes the subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. The health-related QOL was evaluated using the Japanese SF-36 [version 2; Medical Outcomes Trust (Hanover, USA), Health Lab (Hanover, USA), QualityMetric (Lincoln, USA), and Shunichi Fukuhara (iHope International, Kyoto, Japan)]. This tool contains 1 item that evaluates the perceived change in health status, and the remaining 35 items are used to generate 8 subscales of 0-100 that evaluate the physical functioning, role limitations due to poor physical health, bodily pain, general health perception, vitality, social functioning, role limitations because of poor emotional health, and role limitations because of poor mental health. All of the patients were evaluated for the presence of RLS using a written survey that was developed by the International Restless Legs Syndrome Research Group in 2003 (21). The six-item K-6 score was used to evaluate psychological distress. The K-6 is scored from 0 to 24, with a score of 13 or greater indicating that the patient is experiencing psychological distress (22).

Laboratory measurements

Laboratory data and anthropometric measurements were obtained for each subject every 4 weeks during the treatment and every six months after SVR was achieved. The body mass index of each patient was calculated by dividing their weight in kilograms by the square of their height in meters. Laboratory examinations included assessments of the white blood cell count, platelet count (PLT), prothrombin time (PT), and levels of blood urea nitrogen, creatinine, total protein, albumin (ALB), total bilirubin (TB), alanine aminotransferase (ALT), γ-glutamyl transpeptidase, cholinesterase, triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), small dense LDL [sdLDL (23)], fasting plasma glucose, and hemoglobin (HbA1c). Fibrosis-4 (FIB-4) (24) was also calculated.

The Cr- and CysC-based estimated GFRs (eGFRs) (mL/min/1.73 m^2) in women and men were calculated using the equations provided by the Japanese Society of Nephrology for Japanese patients (25). The difference (dGFR) was calculated as follows: Cr-based eGFRs - CysC-based eGFRs. The SI was calculated as follows: Cr/CysC ×100. CBMM was calculated as follows: [body weight (kg) × Cr] / [(K × body weight (kg) × CysC) + Cr)], where K=0.00675 for men and K=0.01006 for women. The CBMM index (CBMMI) was calculated as follows: CBMM / height (m) / height (m).

CT analyses of the body composition

Of the 100 patients, 82 were screened for HCC using CT at the beginning of DAA treatment and 3 years later. Cross-sectional CT images of the third lumbar vertebrae were analyzed using the Slice-O-Matic software program (version 5.0; Tomovision, Montreal, Canada) to determine the SM mass in these 82 patients. Muscle areas included the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis muscles. Tissue Hounsfield unit (HU) thresholds were employed: −29-150 HU for SM; −190 to −30 for subcutaneous adipose tissue (SAT); and −150 to −50 for visceral adipose tissue (VAT) (26). In addition, the mean muscle attenuation (MA) was calculated using the same CT images as had been used to assess the SM quality.

Statistical analyses

Data were analyzed using the StatFlex 6.0 software program (Artech, Osaka, Japan) and were presented as mean ± standard deviation. Laboratory result variables were compared using correlation analyses, t-tests (for differences between two groups), and χ^2 tests. Multi-regression analysis was performed. β is the standardized partial regression coefficient. Multivariate analyses were performed using logistic regression analyses. Correlations were evaluated based on Pearson's correlation coefficient (R); p values <0.05 were considered statistically significant.

Results

Differences in clinical factors and PROs between the beginning of DAA and three years later

Overall, 100 patients were examined in this study (Table 1). Patients with HCV genotype 1b were treated by DCV/ASV and SOF/LDV, and those with genotype 2a and 2b were treated by SOF/RBV. At the beginning of DAA treatment, 38, 5, and 9 patients developed hypertension, hyperlipidemia, and diabetes, respectively. In addition, three patients had Basedow's disease, and one patient had hypothyroid disease as a complication. One patient was treated for rheumatoid arthritis. Two patients had a history of treatment for gastric cancer. Two patients were treated for breast cancer and two patients for colorectal cancer. Human T-cell lymphotropic virus type 1 (HTLV-1)-positive patients (six cases) were diagnosed by the presence of anti-HTLV-1 antibody in the serum. No patients had HCC at the beginning of DAA, except for six patients with a history of HCC. HCC was not detected in the follow-up period. ALT, AST, PLT, and FIB-4 values improved three years later. Cr and Cr-eGFR had increased three years later, but CysC and CysC-eGFR did not change significantly. The SI increased, and the deGFR decreased, but the CBMM did not change significantly. LDL, sdLDL, and HDL levels had increased three years later, but the body weight did not change significantly. In PROs (Table 2), the CSS and PSQI improved, but the K-6 and ESS did not change significantly. Furthermore, the general health perception (GHN) in the SF-36 had significantly improved three years later.

Changes in the GHN were influenced by changes in the CSS, PSQI, and CBMM over three years

The relationship among clinical factors and PROs is presented in Table 3. Changes in the GHN (dGHN) were calculated as follows: dGHN = GHN three years later - GHN at the beginning of treatment. Changes in other factors (dfactors) was calculated in a similar manner. The dGHN was related to the dCSS, dPSQI, dCysC, dCBMM, and dbody weight. In a multi-regression analysis, the dGHN was influenced by the dCSS, dPSQI, and dCBMM.

Changes in symptoms and the association of dGHN with dSymptoms

We compared each factor in the CSS and PSQI between the beginning of treatment and three years later (Table 4). In the CSS, CSS4 (fatigue) and CSS7 (abdominal fullness) had improved by three years later. The dGHN was associated with dCSS4 (fatigue), dCSS5 (decreased strength), and dCSS6 (anxiety). In the PSQI, PSQI1 (subjective sleep quality) and PSQI2 (sleep latency) had improved by three years later. The dGHN was associated with dPSQI1 (subjective sleep quality), dPSQI2 (sleep latency), and dPSQI6 (use of sleep medication).

Table 1. Clinical Profile of 100 Patients with HCV at the Beginning of DAA Treatment and 3 Years Later.

Factors	Start of DAA	3 years later	p value
DAA (DCV/ASV, SOF/LDV, SOF/RBV)	24, 50, 26		
Sustained viral response (%)	**100**		
HCV genotype (1b, 2a, 2b)	74, 21, 5		
HCV-RNA	5.963 (0.925)		
Advanced fibrosis (FIB-4 3.25 over)	**38**		
Age	67.1 (11.29)		
High age (65 over)	65		
Sex (Female, Male)	65, 35		
HCC past history	6		
HTLV-1	13		
Hypertension	38		
Hyperlipidemia	5		
Diabetes	9		
ALT	46.25 (39.1)	17.3 (9.315)	<0.0001
AST	44.99 (28.1)	22.99 (8.448)	<0.0001
PLT	15.85 (6.245)	18.04 (9.925)	0.024
FIB-4	3.711 (3.3)	2.803 (82.62)	<0.0001
Albumin	4.218 (0.482)	4.438 (0.339)	<0.0001
α-fetoprotein	9.972 (13.16)	4.047 (1.851)	<0.0001
Cr	0.789 (0.65)	0.862 (80.52)	0.008
Cr-eGFR	71.22 (17.685)	63.54 (16.69)	<0.0001
CysC	1.256 (0.656)	1.192 (0.87)	0.0905
CysC-eGFR	58.71 (18.37)	70.05 (61.71)	0.0541
SI	0.634 (0.126)	0.75 (0.159)	<0.0001
CBMM	30.81 (87.422)	32.6 (7.141)	0.7963
deGFR	12.26 (13.8)	-6.512 (59.85)	0.0024
LDL	108.18 (830.7)	122.03 (31.45)	<0.0001
sdLDL	20.176 (13.3)	30.33 (14.3)	<0.0001
HDL	62.2 (17.7)	66.12 (817.74)	0.0014
TG	117.13 (77.99)	114.13 (880.43)	0.6047
HbA1c	5.63 (0.55)	5.77 (0.62)	0.0003
Body weight	54.77 (10.7)	54.81 (11.434)	0.7746
BMI	22.55 (4.483)	22.38 (5.26)	0.4838

Data are presented as mean [SD (standard deviation)] or number.

Normal range of clinical parameters in fasting serum: aspartate aminotransferase (AST), 10-40 U/L; alanine aminotransferase (ALT), 5–40 U/L; albumin, 3.8–5.2 g/dL; platelets, male patients (M), 13.1–36.2×10^4/μL; platelets, female patients (F), 13.0–36.9×10^4/μL; low-density lipoprotein (LDL), 70–139 mg/dL; high-density lipoprotein (HDL), M, 40–86 mg/dL; HDL, F, 40–96 mg/dL; triglyceride (TG), 50–149 mg/dL; creatinine, M, 0.61–1.04 mg/dL; creatinine, F, 0.47–0.79 mg/dL; ferritin, M, 39.4–340 ng/mL; ferritin, F, 3.6–114 ng/mL; and hemoglobin (HbA1c), 4.6–6.2%; α-fetoprotein (AFP), not over 10.0 ng/mL; cystatin C (CysC), M, 0.3-0.95 mg/L, F, 0.56-0.87 mg/L. All laboratory data measurements were undertaken after overnight fasting.

DAA: direct acting antiviral, deGFR: difference between CrGFR and CysCGFR

Changes in the GHN were influenced by change in the SM mass

Since dGHN is influenced by the CBMM, changes in the SM mass were evaluated by CT in 82 of 100 patients. Three years later, the SM and muscle attenuation (MA) had decreased, whereas the intramuscular adipose tissue (IMAT), VAT, and SAT had increased. However, the dGHN was positively associated with the dSM and dSAT and tended to have an association with the dVAT. In a multi-regression analysis, the dGHN was influenced by the dSM only.

The GHN deteriorated in patients with RLS at the beginning

Finally, we explored the factors associated with the deterioration GHN. Factors pre-DAA treatment were compared between the two groups (Supplementary material 1). For each PRO, a sick status was assigned to severely affected patients. A poor sleeper had ≥10 points on the ESS and ≥6 points on the PSQI. We previously showed that MHE was correlated with ≥9 points on the CSS (27). Psychological distress is defined as ≥13 points on the K-6.

Table 2. Changes in Scores of PROs in Patients with HCV Infection from the Beginning of Treatment to 3 Years Later.

	Start of DAA	3 years later	p value
CSS	6.2 (4.158)	5.13 (4.032)	0.0084
K-6	2.36 (2.993)	2.03 (3.483)	0.3311
PD in K-6	2	3	1
ESS	3.51 (83.189)	3.56 (3.295)	0.8509
PSQI	6.89 (3.256)	6.3 (2.721)	0.0391
RLS	13	9	0.4986
SF-36:PFN	43.6 (12.614)	42.47 (14.824)	0.3599
SF-36:RPN	43.78 (12.24)	45.03 (12.28)	0.378
SF-36:BPN	48.87 (10.9)	48.99 (10.61)	0.8163
SF-36:GHN	43.54 (89.09)	47.35 (8.08)	<0.0001
SF-36:VTN	48.6 (10.97)	49.25 (9.6)	0.5487
SF-36:SFN	47.15 (11.234)	49.19 (9.49)	0.0996
SF-36:REN	45.22 (12.59)	47.12 (12.1)	0.1311
SF-36:MHN	50.75 (9.43)	49.21 (9.14)	0.1571
SF-36:PCS	43.11 (12.53)	43.49 (12.73)	0.6908
SF-36:MCS	50.9 (8.831)	51.87 (8.387)	0.3278
SF-36:RCS	47.36 (12.06)	48.19 (11.55)	0.6383

Data are presented as mean (SD).

CSS: Cirrhosis-related symptom score, ESS: Epworth sleepiness score, K-6: Kessler 6 score, PRO: patient-reported outcome, PSQI: Pittsburgh sleep quality index, BPN: bodily pain, SF-36, GHN: general health, MCS: mental component summary, MHN: mental health, NS: not significant, PCS: physical component summary, PFN: physical functioning, RCS: role/social component summary, REN: role emotional, RPN: role physical, SFN: social functioning, VTN: vitality, RLS: restless legs syndrome, PD: psychological distress

Table 3. dGHN and dFactors.

	Relation to dGHN		Multi-regression analysis for dGHN	
	R	p value	β	p value
dCSS	-0.266	0.0079	-0.335	0.0008
dPSQI	-0.344	0.0005	-0.4	<0.0001
dLDL	-0.076	0.462		
dHDL	-0.09	0.3803		
dHbA1c	0.04	0.6978		
dCreGFR	0.08	0.435		
dCr	0.068	0.5063		
dCysCeGFR	-0.068	0.5251		
dCysC	-0.361	0.0005	-0.057	0.5718
dFIB	0.049	0.6317		
dSI	0.142	0.1869		
ddGFR	0.084	0.437		
dCBMM	0.212	0.043	0.297	0.0055
dsdLDL	0.115	0.2883		
dbody weight	0.23	0.023	0.119	0.2283
dBMI	0.116	0.2558		

The dfactors is the difference in the value of factor between the beginning of DAA and 3 years later (dfactors=value of factor 3 years later -value at the beginning of DAA).

R is the correlation coefficient.

β is the standardized partial regression coefficient.

dLDL (mg/dL), dHDL (mg/dL), dHbA1c (%), dCreGFR (mL/min/1.73 m^2), dCr (mg/dL), dCysCeGFR (mL/min/1.73 m^2), dCysC (mg/L), dsdLDL (mg/dL), dbody weight (kg), dBMI (kg/m^2)

FIB: fibrosis-4, dGFR: deGFR

The presence of RLS was defined by the RLS criteria. We previously reported that the receiver operating characteristic (ROC) curve analysis between sarcopenia and CBMM revealed an area under the ROC curve of 0.78504 in women and 0.86067 in men, and the cut-off CBMM values for sarcopenia were 27.903 in women and 39.731 in men with chronic liver disease (28). The sex, HCV genotype, DAAs, age (<65 years old), minimal hepatic encephalopathy (MHE; 22 cases), poor sleeper according to the ESS (4 cases), RLS (13 cases), psychological distress (PD) in K-6 (2 cases), and sarcopenia in CBMM (women, <28; men, <40; 70 cases) were not significantly associated with the dGHN. Developed hypertension, poor sleepers according to the PSQI (38 cases), and low FIB-4 (less than 3.25; 63 cases) significantly increased with the dGHN.

In addition, factors at three years after starting treatment were compared between the two groups (Supplementary material 2). Poor sleepers according to the PSQI at 3 years (40 cases), MHE at 3 years (18 cases), RLS at 3 years (9 cases), and sarcopenia in CBMM at 3 years (55 cases) were not significantly associated with the dGHN. Poor sleepers according to the ESS at 3 years (4 cases), PD at 3 years (3 cases), and low FIB-4 at 3 years (77 cases) significantly increased with the dGHN. In a univariate logistic regression analysis for deterioration of the dGHN (<0), RLS at start, a low FIB-4 at start, and low age were contributing factors (odds ratio: 5.5568, 0.0275, and 0.329, respectively). In a multivariate logistic regression analysis, age was excluded from the analysis, as the FIB-4 levels and dGHN did not differ markedly between the high and low age groups (Supplementary material 1E). The presence of RLS and low FIB-4 levels at the beginning of treatment were factors contributing to the deterioration of the dGHN (odds ratios, 6.22 and 0.325; 95% confidence intervals, 1.722-22.471 and 0.123-0.855; and p = 0.0053 and 0.028, respectively).

Discussion

Three years later, the GHN on the SF-36 had improved since starting DAA. Changes in GHN were related to an improved sleep quality on the PSQI and CSS. In addition, the dGHN was positively related to the dSM. The sleep quality, sleep latency, and fatigue were related to the dGHN. RLS and FIB-4 contributed to the deterioration of the GHN. We previously reported that HCV-related symptoms, but not the QOL, were improved by DAA one year after starting the treatment (9). In this study, we showed an improvement in the GHN on the SF-36 in addition to the improvement of the symptoms three years after treatment. Previous reports have evaluated the improvement of the QOL at one year after treatment in industry-sponsored registration trials. This is the first report to evaluate the real-world impact of DAAs

Table 4. Changes in Symptom Markers in Patients with HCV Infection from the Beginning of DAA to 3 Years Later.

				Relation with dGHN and dfactors	
	Start of DAA	3 years after	p value	R	p value
CSS1: hand tremor	0.26 (0.548)	0.198 (0.515)	0.3199	-0.118	0.2588
CSS2: appetite loss	0.564 (0.564)	0.693 (0.693)	0.779	-0.147	0.1589
CSS3: foot muscle cramps	0.813 (0.654)	0.688 (0.621)	0.0832	0.179	0.0847
CSS4: fatigue	0.927 (0.861)	0.667 (0.743)	0.0011	-0.308	0.0024
CSS5: decreased strength	1.177 (0.781)	1.052 (0.863)	0.1755	-0.378	0.0001
CSS6: anxiety	0.744 (0.744)	0.573 (0.677)	0.1601	-0.342	0.0007
CSS7: abdominal fullness	0.573 (0.692)	0.417 (0.61)	0.0464	0.027	0.798
CSS8: abdominal pain	0.365 (0.484)	0.281 (0.496)	0.145	-0.09	0.3879
CSS9: a feeling of low energy	0.948 (0.716)	0.844 (0.759)	0.2775	-0.082	0.433
PSQI1: subjective sleep quality	1.163 (0.669)	0.99 (0.611)	0.0187	-0.258	0.0109
PSQI2: sleep latency	0.98 (0.932)	0.77 (0.79)	0.0132	-0.225	0.0258
PSQI3: sleep duration	1.17 (0.842)	1.22 (0.894)	0.6312	-0.182	0.0722
PSQI4: habitual sleep efficiency	0.616 (0.987)	0.515 (0.896)	0.5435	-0.018	0.8606
PSQI5: sleep disturbance	1.77 (0.52)	1.673 (0.552)	0.1143	-0.117	0.2562
PSQI6: use of sleep medication	0.79 (1.266)	0.776 (81.266)	0.6705	-0.331	0.0008
PSQI7: daytime dysfunction	0.42 (0.589)	0.418 (0.798)	0.9005	0.023	0.8281

Date are presented as mean (SD).

R is the correlation coefficient between dGHN and dfactors. CSS: cirrhosis-related symptom score, PSQI: pittsburg sleep quality index

on the QOL of patients with HCV infection three years after starting DAA treatment.

The PSQI and CSS were PROs for the evaluation of the sleep quality and CSS, respectively. DAA treatment improved the PSQI and CSS, and these improvements were associated with the improvement of the QOL (Table 2, 3). Changes in HCV-related extra-hepatic symptoms treated by DAAs were reported previously (29). Sleep disturbance and fatigue are particularly common symptoms in patients with HCV infection (6, 7). In the present study, the sleep quality, sleep latency, and fatigue showed significant improvements after three years (Table 4). Therefore, we believe that sleep latency and fatigue are reference index symptoms in HCV-related extra-hepatic symptoms for the observation of the QOL. In contrast, psychological distress in K-6 and RLS did not improve markedly after three years of DAA treatment (Table 2). We previously reported that PD and RLS were decreased by DAAs over a period of one year (9). However, we speculated that PD and RLS were difficult to improve by DAA in the long term. Extra-hepatic symptoms were related to the deterioration of the QOL (7), and our study suggested that the improvement of extra-hepatic symptoms was related to the improvement of the QOL.

In this study, improvement of the QOL was related to increased SM. Previously, DAA treatment increased the SMI in patients with a low SM mass (15), and chronic HCV infection caused a decrease in the SM mass (14). A low muscle mass was related to a poor QOL in patients with chronic liver disease (11) and advanced cancer (30). Subjects with sarcopenia showed an extremely high proportion of problems relating to several dimensions of the QOL (12). Sarcopenia is a harmful condition in patients with chronic liver disease (10). We previously reported that CBMM contributed to the muscle mass, grip strength, and sarcopenia in patients with chronic liver disease (28). Although we did not explore grip strength in the present study, as one of the criteria for sarcopenia, the difference in the CBMM between the beginning of treatment and three years later contributed to the difference in the GHN (Table 3). In addition, the differentiation of SM contributed to the dGHN in 82 patients (Table 5). We concluded that increasing muscle mass contributed to the improvement in the QOL in this study. For to further improve the QOL, we recommend exercise and diet to increase the muscle mass along with DAA treatment in patients with HCV infection.

To increase the cost-effectiveness of DAA treatment, it is necessary to take measures to improve the QOL of patients after SVR (5). Therefore, we analyzed the factors contributing to the deterioration of the GHN (Table 6). The presence of RLS and low FIB-4 at the beginning of treatment and a young age were factors contributing to the deterioration of the GHN in a univariate analysis. In a multivariate analysis, the presence of RLS and low FIB-4 levels at the beginning of treatment were contributing factors. Bonkovsky et al (31). found that advanced fibrosis was strongly associated with a decline in the QOL. Our study findings indicated that patients with advanced fibrosis tended to show amelioration of the QOL. No relationship between the dGHN and dFIB was demonstrated (Table 3), but this relationship needs to be observed over a prolonged period. Previous studies indicated that a young age (35-65 years old) was a predictor of PRO improvement (7), but liver fibrosis did not predict PRO im-

Table 5. Changes in Body Composition and Relation with dGHN and dSM.

	Beginning of DAA	3 years later	p value	Relation with dGHN and dfactors R	p value	Multi-regression analysis for dGHN β	p value
SM	102.4 (26.05)	98.17 (73.0)	0.0316	0.337	0.0062	0.283	0.0275
IMAT	5.47 (4.187)	8.35 (6.46)	<0.0001	0.026	0.8407		
VAT	75.93 (66.9)	90.167 (73.9)	<0.0001	0.234	0.0627	0.111	0.4946
SAT	110.1 (53.85)	111.54 (53.5)	0.042	0.284	0.0225	0.122	0.4688
MA	31.27 (5.94)	29.39 (6.03)	<0.0001	0.194	0.146		

Data are presented as mean (SD).

R is the correlation coefficient with dGHN and dfactors.

β is the standardized partial regression coefficient.

SM, IMAT, VAT and SAT (cm^2), MA (HU)

SM: Skeletal muscle mass, IMAT: intramuscular adipose tissue, VAT: visceral adipose tissue, SAT: subcutaneous adipose tissue, MA: muscle attenuation, HU: Hounsfield unit

Table 6. Deterioration of GHN and Clinical Factors.

	Univariate analysis			Multivariate analysis		
Factor	Odds ratios	95% CI	p value	Odds ratios	95% CI	p value
RLS at start	5.5568	1.627–18.986	0.0062	**6.22**	**1.722-22.471**	**0.0053**
RLS at 3Y	3.884	0.808–18.674	0.0903			
MHE at start	2.923	0.788–10.837	0.1086			
MHE at 3Y	0.996	0.315–3.091	0.981			
Poor/PSQI at start	0.445	0.18–1.099	0.0791			
Poor/PSQI at 3Y	1.174	0.471–2.926	0.7309			
Male	0.414	0.149–1.151	0.091			
GT2a/2b	0.278	0.076–1.023	0.0541			
FIB-4 Low at start	0.0275	0.144–0.893	0.0275	**0.325**	**0.123-0.855**	**0.028**
CBMM Low at start	1.143	0.418–3.122	0.7945			
Age Low	0.329	0.112–0.97	0.043			

FIB-4 Low group is less than 3.25.

CBMM Low group is less than 28 in women and less than 40 in men.

Low age group, age<65 years

CI: confidence interval

provement (32). Although our study included many older (> 65 years old) patients (65 cases in Table 1), old age was not found to be related to the deterioration of the GHN (Supplementary material 1E). The factors that contributed to worsening of the CSS were HCV genotype 2b and RLS one year after the start of treatment. Furthermore, while RLS had improved by one year after treatment (9), but there was no marked change after three years (Table 2). The relationship between HCV infection and RLS was not clarified, and the frequency of RLS was not markedly different at the initiation of treatment and three years after treatment in this study. However, since RLS influenced the QOL in patients with chronic liver disease (33), we believe that the presence of RLS is a predictive factor for a poor QOL. When RLS is diagnosed at the beginning of DAA treatment by PRO, we should consider treatment of RLS in addition to DAA administration to improve the QOL.

This study has several limitations including the small sample size (100 cases) and the evaluation of the body composition by CT in only some cases (82 out of 100). Furthermore, the grip strength was not evaluated for the diagnosis of sarcopenia. In addition, patients had various complications before starting DAA therapy. We used the CSS for the evaluation of symptoms, as it can be used to assess MHE with and without cirrhosis (27). Aside from the CSS, a disease-specific questionnaire to measure the health-related QOL of patients with chronic liver disease (34) is needed in the future.

However, this study evaluated the real-world clinical impact of DAA treatment over a long interval. Along with a previous report (7) that reported that the QOL was related to HCV-related symptoms (sleep disturbance and several other symptoms), our study suggests that improvement of the QOL is related to increases in the muscle volume by DAA treatment. For the further improvement of the QOL and cost-effectiveness of DAA treatment, the treatment of RLS and increment of muscle volume are necessary in patients with HCV infection undergoing DAA treatment.

The authors state that they have no Conflict of Interest (COI).

References

1. Huang CF, Iio E, Jun DW, et al. Direct-acting antivirals in East Asian hepatitis C patients: real-world experience from the REAL-C Consortium. Hepatol Int **13**: 587-598, 2019.
2. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet **6736**: 1-12, 2019.
3. Chhatwal J, He T, Hur C, et al. Direct-acting antiviral agents for patients with hepatitis C virus genotype 1 infection are cost-saving. Clin Gastroenterol Hepatol **15**: 827-837.e8, 2017.
4. He T, Lopez-Olivo MA, Hur C, et al. Systematic review: cost-effectiveness of direct-acting antivirals for treatment of hepatitis C genotypes 2-6. Aliment Pharmacol Ther **46**: 711-721, 2017.
5. Kaishima T, Akita T, Ohisa M, et al. Cost-effectiveness analyses of anti-hepatitis C virus treatments using quality of life scoring among patients with chronic liver disease in Hiroshima prefecture. Japan Hepatol Res **48**: 509-520, 2018.
6. Evon DM, Stewart PW, Amador J, et al. A comprehensive assessment of patient reported symptom burden, medical comorbidities, and functional well being in patients initiating direct acting antiviral therapy for chronic hepatitis C: Results from a large US multicenter observational study. PLoS One **13**: 1-26, 2018.
7. Evon DM, Sarkar S, Amador J, et al. Patient-reported symptoms during and after direct-acting antiviral therapies for chronic hepatitis C: The PROP UP study. J Hepatol **71**: 486-497, 2019.
8. Saeed S, Moodie EEM, Strumpf E, et al. Real-world impact of direct acting antiviral therapy on health-related quality of life in HIV/Hepatitis C co-infected individuals. J Viral Hepat **25**: 1507-1514, 2018.
9. Ichikawa T, Miyaaki H, Miuma S, et al. Hepatitis C virus-related symptoms, but not quality of life, were improved by treatment with direct-acting antivirals. Hepatol Res **48**: 1-8, 2017.
10. van Vugt JLA, Alferink LJM, Buettner S, et al. A model including sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant candidates: a competing risk analysis in a national cohort. J Hepatol **68**: 707-714, 2018.
11. Ohashi K, Ishikawa T, Imai M, et al. Relationship between presarcopenia and quality of life in patients with chronic liver disease. Eur J Gastroenterol Hepatol **31**: 1, 2019.
12. Tsekoura M, Kastrinis A, Katsoulaki M, et al. Sarcopenia and its impact on quality of life. In: Advances in Experimental Medicine and Biology. 2017: 213-218.
13. Takata R, Nishikawa H, Enomoto H, et al. Relationship between skeletal muscle mass and liver fibrosis markers for patients with hepatitis C virus related liver disease. Medicine (Baltimore) **96**: 1-8, 2017.
14. Gowda C, Compher C, Amorosa VK, et al. Association between chronic hepatitis C virus infection and low muscle mass in U.S. adults. J Viral Hepat **21**: 938-943, 2014.
15. Sugimoto R, Iwasa M, Hara N, et al. Changes in liver function and body composition by direct-acting antiviral therapy for hepatitis C virus infection. Hepatol Res **48**: 337-344, 2018.
16. Kashani KB, Frazee EN, Kukrálová L, et al. Evaluating muscle mass by using markers of kidney function: development of the sarcopenia index. Crit Care Med **45**: 1-7, 2016.
17. Kim SW, Jung HW, Kim CH, et al. A new equation to estimate muscle mass from creatinine and cystatin C. PLoS One **11**: 1-9, 2016.
18. Ichikawa T, Miyaaki H, Miuma S, et al. Indices calculated by serum creatinine and cystatin C as predictors of liver damage, muscle strength and sarcopenia in liver disease. Biomed REPORTS **12**: 89-98, 2020.
19. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep **14**: 540-545, 1991.
20. Doi Y, Minowa M, Uchiyama M, et al. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. Psychiatry Res **97**: 165-172, 2000.
21. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med **4**: 101-119, 2003.
22. Kessler RC, Andrews G, Colpe LJ, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med **32**: 959-976, 2002.
23. Ichikawa T, Miyaaki H, Miuma S, et al. Carotid intima-media thickness and small dense low-density lipoprotein cholesterol increase after one year of treatment with direct-acting antivirals in patients with hepatitis C virus infection. Intern Med **58**: 1209-1215, 2019.
24. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and FibroTest. Hepatology **46**: 32-36, 2007.
25. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis **53**: 982-992, 2009.
26. Fujiwara N, Nakagawa H, Kudo Y, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. J Hepatol **63**: 131-140, 2015.
27. Yoshimura E, Ichikawa T, Miyaaki H, et al. Screening for minimal hepatic encephalopathy in patients with cirrhosis by cirrhosis-related symptoms and a history of overt hepatic encephalopathy. Biomed Rep **5**: 193-198, 2016.
28. Ichikawa T, Miyaaki H, Miuma S, et al. Calculated body muscle mass as a useful screening marker for low skeleton muscle mass and sarcopenia in chronic liver disease. Hepatol Res **2020**: hepr.13492, 2020.
29. Ioannou GN, Feld JJ. What are the benefits of a sustained virologic response to direct-acting antiviral therapy for hepatitis C virus infection? Gastroenterology **156**: 446-460.e2, 2019.
30. Nipp RD, Fuchs G, El-Jawahri A, et al. Sarcopenia is associated with quality of life and depression in patients with advanced cancer. Oncologist **23**: 97-104, 2018.
31. Bonkovsky HL, Snow KK, Malet PF, et al. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. J Hepatol **46**: 420-431, 2007.
32. Sung JC, Bosh C, Wyatt B, et al. Hepatitis C cure improved patient-reported outcomes in patients with and without liver fibrosis in a prospective study at a large urban medical center. J Viral Hepat **27**: 350-359, 2020.
33. Matsuzaki T, Ichikawa T, Kondo H, et al. Prevalence of restless legs syndrome in Japanese patients with chronic liver disease. Hepatol Res **42**: 1221-1226, 2012.
34. Younossi ZM, Guyatt G, Kiwi M, et al. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut **45**: 295-300, 1999.