Hepatitis C virus-related symptoms, but not quality of life, were improved by treatment with direct-acting antivirals

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Abbreviations:

LC, liver cirrhosis; DM, diabetes mellitus; T2DM, type 2 diabetes mellitus; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; GA, glycated albumin; HCV, hepatitis C virus; Cr, creatinine; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein

cholesterol; DAA, direct acting antivirals; DCV, daclatasvir; ASV, asunaprevir; ALT, alanine aminotransferase; CH, chronic hepatitis; LC, liver cirrhosis; SOF, sofosbuvir; RIB, ribavirin; LDV, ledipasvir; ESS, Epworth sleep score; PSQI, Pittsburg sleep quality index; RLS, restless legs syndrome; HT, hypertension; AFP, α-fetoprotein.

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ABSTRACT

Background & aims: Direct acting-antivirals (DAAs) for treating hepatitis C virus (HCV) infection have a significant high sustained viral response rate after a short treatment course and do not have any severe adverse effects. Patient-reported outcomes (PROs) have become increasingly important to assess the total impact of a chronic disease. We aimed to evaluate the changes in symptoms of patients with HCV infection treated with DAA by using PROs.

Methods: A total of 107 patients with chronic HCV infection were treated with DAAs. Daclatasvir/asunaprevir or sofosbuvir/ledipasvir was used for HCV 1B infection, and sofosbuvir/ribavirin for HCV 2A/2B infection. The PROs measured at the start of treatment and a year after the start of treatment were cirrhosis-related symptom score (CSS), presence of restless legs syndrome (RLS), Epworth sleepiness score (ESS), Pittsburg sleepiness quality index (PSQI), Kessler 6 score (K-6), and the SF-36 to measure quality of life (QOL). All patients had a sustained viral response rate of 24.

Results: CSS, PSQI, K-6, and RLS scores were improved 1 year after beginning treatment. However, QOL had not recovered. Changes in total CSS were correlated with HCV genotype, sex, hypertensive drug use, serum LDL, and ESS at the start of treatment and RLS a year after the start of treatment. The factors that contributed to

worsening of CSS were HCV genotype 2B and RLS a year after the start of treatment.

Conclusions: DAA treatment disappeared HCV-RNA and improved most symptoms, but QOL did not recover.

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INTRODUCTION

Direct-acting antivirals (DAA) changed hepatitis C virus (HCV) infection treatment recently. Daclatasvir/asunaprevir (DCV/ASV) [1] and sofosbuvir/ledipasvir (SOF/LDV) [2] for HCV 1B infection and sofosbuvir/ribavirin (SOF/RIB) for HCV 2A/2B infection [3] are common DAA treatments in Japan. These treatments have significant high sustained viral response (SVR) rates (85–100%) after a short treatment course (12–24 weeks) and do not have any severe adverse effects.

Patient-reported outcomes (PROs), including health-related quality of life (QOL), have become increasingly important to assess the total impact of a chronic disease or an intervention on patient health and well-being [4]. Interferon-based HCV treatment leads to lower QOL (as measured by the SF-36) in the period of treatment but it recovers to pre-treatment levels 12 weeks later, whereas DAA treatment does not decrease QOL scores in the period of treatment and it remains the same at the start of treatment and 12 weeks after discontinuation of treatment [5]. Interestingly, QOL is impaired in patients with viral clearance after interferon but not after spontaneous clearance [6]. However, various PROs, such as the HCV-specific Quality of Life Chronic Liver Disease Questionnaire-HCV version, Functional Assessment of Chronic Illness Therapy-Fatigue, and Work Productivity and Activity Index have improved

scores 12 weeks after patients discontinue treatment with DAA [7]. Different PROs measure different factors. Therefore, PRO instruments that specifically capture the effect of HCV infection on QOL will be needed in the new treatment era [8].

We have reported several PROs related to chronic liver disease. The cirrhosis-related symptom score (CSS), used for total evaluation of chronic liver disease, is correlated with the Child-Pugh score and minimal hepatic encephalopathy [9]. The restless legs syndrome (RLS) is a common complication of cirrhosis and affects sleep status as evaluated by the Pittsburg sleepiness quality index (PSQI) and the quality of life (QOL) evaluated by the SF-36 [10]. The Epworth sleepiness score (ESS) in patients with cirrhosis can be improved by ingestion of branched chain amino acid supplements [11]. Previously, we used these PROs and could evaluate changes in symptoms in response to liver transplantation and supplementation [12].

To evaluate the changes in symptoms of patients treated with DAA, we used these PROs in this study. Additionally, for evaluation of psychological distress, we added the Kessler 6 score (K-6) [13] to this PROs set.

PATIENTS AND METHODS

Patients

One hundred seven patients with chronic infection with HCV genotype 1B, 2A, and 2B with chronic hepatitis and compensatory cirrhosis were treated with DAAs, DCV/ASV (Bristol-Myers Squibb Co. Ltd., Tokyo, Japan) or SOF/LDV (Gilead Sciences Co. Ltd., Tokyo, Japan) for 1B and SOF/RIB for 2A/2B (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) at Nagasaki Harbor Medical Center from June 2014 to November 2016. Combination therapy with DCV/ASV was orally administered for 24 weeks [1] and SOF/LDV and SOF/RIB were orally administered for 12 weeks [2, 3]. During the treatment period, serum HCV-RNA was examined every 4 weeks; after the end of the treatment period, these measurements were performed every 12 weeks. SVR was determined at 24 weeks after the end of treatment. At week 24 after the end of treatment, an SVR was achieved in all patients.

PROs were evaluated at the start of treatment and 1 year after the start of treatment. At the start of treatment, patients were asked about their use of medications for abnormal lipids, hypertension, diabetes, and gout. Informed consent was obtained from each patient included in the study, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as evidenced by the approval of the

study by the Human Research Ethics Committee of Nagasaki Harbor Medical Center (NIRB 1512003).

Patient-reported outcomes

The CSS questionnaire contains items regarding cirrhotic symptoms, which include hand tremors (CSS1), appetite loss (CSS2), foot muscle cramps (CSS3), fatigue (CSS4), decreased strength (CSS5), anxiety (CSS6), abdominal fullness (CSS7), abdominal pain (CSS8), and a feeling of low energy (CSS9). An "impact factor" for each item was calculated, which was defined as the product of the frequency of the item and the mean importance that the patients attributed to the item. The impact factor for each item ranged from 0 to 3, and the CSS was calculated as the sum of the impact factors [9, 11, 12]. The Epworth Sleepiness Scale [ESS] [14] was used to evaluate daytime hypersomnolence; ESS scores range from 0 to 24, and a score of ≥ 10 indicates significant daytime hypersomnolence. Sleep quality was evaluated using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) [15, 16]. Responses to the PSQI questionnaire were used to generate seven components, which were scored from 0 (normal) to 3 (extremely poor). Health-related quality of life was evaluated using the Japanese SF-36 (version 2; Medical Outcomes Trust [Hanover, NH, USA], Health Lab [Hanover, NH, USA], QualityMetric [Lincoln, RI, USA], and Shunichi Fukuhara

[iHope International; Chuo Ward, Kyoto, Japan]). This tool contains 1 item that evaluates the perceived change in health status, and the remaining 35 items are used to generate eight subscales of 0–100 that evaluate 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. Patients were diagnosed with RLS if they fulfilled all four criteria and exhibited symptoms of RLS that occurred at least twice per week. 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 categorized as the patient experiencing psychological distress [17].

Laboratory measurements

Laboratory data and anthropometric measurements were obtained for each subject every 4 weeks during treatment and every 12 weeks after treatment. The body mass index (BMI) of each patient was calculated from their weight in kg divided by the square of their height in meters. Laboratory examinations included assessment of the white blood cell count, platelet count, prothrombin time, hemoglobin, C-reactive protein,

blood urea nitrogen, creatinine, total protein, albumin, total bilirubin, alanine aminotransferase, γ-glutamyl transpeptidase, cholinesterase, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL), fasting plasma glucose, and hemoglobin (HbA1c).

Statistical analysis

Data were analyzed using StatView 5.0 software (SAS Institute Inc., Cary, NC, USA). Laboratory result variables were compared using correlation analysis, *t*-tests, and χ^2-square tests. Correlations were evaluated with coefficients of correlation. Multivariate analysis was performed with logistic regression tests. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Clinical profiles at the start of DAA treatment were generally not different among groups (Table 1). The mean age of the patients treated with SOF/RIB was lower than that of patients in other groups and serum albumin concentration in the group treated with DCV/ASV was lower than that in the SOF/LDV group. Platelet counts in the DCV/ASV group were higher than the other groups. However, other clinical factors, including medication use, were not different among groups.

Changes in symptoms evaluated by PROs from the start of DAA treatment to 1 year after treatment are summarized in Table 2. The total CSS is summed from CSS1 to CSS9. CSS3–9 and total CSS were improved at 1 year of follow up. Similarly, K-6 and PSQI were also improved at 1 year. Thus, liver disease-related symptoms (CSS), psychological distress (K-6), and sleep disturbances (PSQI) improved in the 1 year after treatment with DAA.

For each PRO, a sick status was defined as more severely affected patients. A poor sleeper had 10 or more points on the ESS and 6 or more points on the PSQI. We have previously shown that minimal hepatic encephalopathy is correlated with 9 or more points on the CSS [9]. Psychological distress is defined as 13 points or more on the K-6. The presence of RLS was defined by RLS criteria. In the 107 patients, poor

sleepers, minimal hepatic encephalopathy, psychological distress, and RLS were improved from the start of DAA to 1 year after (Table 3). However, QOL, evaluated by the SF-36, was not different at the 1-year follow up (Table 4).

Next, we paid attention to changes in total CSS. Scores at 1 year were subtracted from the score at the start of DAA to obtain the change in CSS. Several clinical factors correlated with changes in total CSS were found (Figure). Among lifestyle-related diseases, hypertension medication users showed greater improvement than non-users (Figure A). Serum LDL levels at the start of DAA were higher in patients with worsening CSS scores than in the CSS recovery group (Figure B). Patients carrying the HCV genotype 2B had less recovery than those with 1B and 2A (Figure C), but the type of DAA was not related to changes in total CSS (Figure D). Poor sleepers by ESS at the start of DAA had greater improvements in total CSS score than normal sleepers (Figure E), and those with RLS at 1 year had worse CSS scores (Figure F). Women experienced greater improvements in CSS than men (Figure G). The other clinical factors in our study were not related to changes in total CSS at 1 year.

We also evaluated factors correlated with CSS deterioration (Table 5A) and improvement (Table 5B). Candidate factors were selected from the previous analysis: HCV genotype 1B and 2A (non2B), non-hypertension drug users (HT−), serum LDL

levels at the start of DAA (LDL0), male sex, ESS scores at the start of DAA (ESS0), and RLS at 1 year (RLS1Y). The factors that contributed to CSS worsening were HCV genotype 2B and RLS at 1 year, but we did not detect any factors correlated with CSS improvement.

DISCUSSION

In this study, liver-related symptoms, sleep disturbance, psychological distress and RLS in patients with HCV infection treated with DAA were improved 1 year after beginning treatment. However, QOL did not recover. Changes in total CSS were correlated with HCV genotype, sex, hypertension drug use, elevated serum LDL at the start of treatment, poor sleeper at the start of treatment, and RLS 1 year after the start of treatment. Factors contributing to CSS worsening were HCV genotype 2B and RLS at 1 year.

Our patients' experienced improvements in symptoms-related scores but did not experience changes on the SF-36 score from the start of DAA treatment to 1 year after. It has been previously reported that SF-36 scores were not improved by interferon and DAA [4, 5, 6, 7]. However, patients with spontaneous clearance of HCV infection have shown improved SF-36 scores [6, 18] and patients with treatment eradication of HCV also show improved SF-36 scores [19]. In our study, the patients were the older (Table 1) than those in reports with improved SF-36 scores (6.18). We speculated that the high age of the patients influenced the improvement in SF-36 score by DAA treatment. Changes in SF-36 induced by treatment were primarily evaluated only 12 weeks after the end of treatment [4, 5, 7]. We speculated that the patients were

evaluated by the SF-36 several years after spontaneous clearance. DAA induced improvement of HCV infection-related symptoms, including foot muscle cramps, fatigue, decreased strength, anxiety, abdominal fullness, abdominal pain, a feeling of low energy, sleep disturbance, psychological distress, and RLS, but it may require several years after relief from these symptoms for an effect on QOL to become apparent. In a future study, patients in whom HCV was eradicated should be observed carefully for QOL and other symptoms, and those who did not recover after DAA should also be evaluated at longer follow-up times.

It is clear from our study that daytime somnolence and sleep disturbances in patients with HCV infection were ameliorated by DAA. RLS also causes sleep disturbances. The overall prevalence of RLS among inhabitants of Ajimu in Japan aged ≥ 65 years is 0.96% and the prevalence of RLS is lower in Japan than in studies conducted in European and North American populations [20]. Previously, we reported that 25 of 149 patients with chronic liver disease (16.8%) fulfilled the diagnostic criteria for RLS [10]. The frequency of HCV infection and interferon treatment that were correlated with RLS onset [21, 22] were also not significantly different between the RLS and non-RLS groups [10]. Patients with RLS often recovered after DAA treatment, but patients that did not recover from RLS did not experience improvements in their

CSS score. We think that patients with HCV infection should have more attention paid to RLS and treatment for RLS after HCV clearance by DAA may be effective in making changes in CSS.

In our study, several problems with extrahepatic symptoms have been clarified. In previous studies, QOL in HCV infected patients has been shown to be correlated with underlying comorbidities, income, and marital status and is not correlated with stage [19, 23]. Because a sex difference was found in changes in CSS, social background factors also should be evaluated. In this study, the underlying comorbidities (abnormal lipid levels, hypertension, diabetes, and gout) were not related to the change in SF-36 score and CSS. HCV genotype 2B was found to be a contributing factor for CSS worsening. However, differences in symptoms by HCV genotype have not been fully evaluated in previous studies. The stage of liver fibrosis and the infecting genotype are not commonly associated with neurocognitive alterations in HCV infection [24]. However, it has been reported recently that patients infected with HCV genotype 3 are at higher risk for end-stage liver disease, hepatomas, and liver-related death [25]. Thus, differences in genotypes should also be paid attention to when evaluating symptoms.

Additionally, HCV-related encephalopathy is not correlated with viral status but is correlated with cognitive dysfunction [26] and sleep disturbance [27]. Because

poor sleepers after SVR are at risk of HCV-related encephalopathy, we should be following up HCV-cleared patients.

Serum LDL at the start of DAA treatment is also correlated with changes in CSS. LDL may affect HCV-RNA replication [28], dietary cholesterol intake is associated with progression of liver disease in patients with HCV infection [29], and the APOE-ε4 allele is protective against attention deficits in HCV-infected individuals [30]. Thus, a full explanation of the relationship between lipids and CSS is still lacking. DAA treatment cleared HCV-RNA in patients, but symptoms and QOL did not fully recover in patients with elevated LDL at baseline. For amelioration of QOL, lingering HCV-related symptoms should be explored. The limitations of our study were the small sample size, single-institution data, and 1-year observation period. These limitations should be considered in future studies.

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Table 1. Clinical profile of 107 patients before DAA treatment

Parameter	DCV/ASV (35)	SOF/LDV (39)	SOF/RIB (33)	p value
HCV genotype	35/1B	39/1B	28/2A, 5/2B	
HCV-RNA	5.883 (0.934)	6.108 (0.746)	5.761 (1.063)	NS
Age	70.829 (11.506)	69.487 (9.467)	63.091 (13.494)	**0.0131 ***0.0213
F/M	24/11	27/12	18/15	NS
CH/LC	22/13	30/9	23/10	NS
ALT	39.714 (35.799)	41.718 (24.408)	55.485 (41.145)	NS
Albumin	4.057 (0.316)	4.308 (0.439)	4.152 (0.496)	*0.0067
Creatinine	0.7339 (0.247)	0.744 (0.149)	0.738 (0.159)	NS
Platelet	20.029 (6.6)	14.618 (5.328)	15.518 (5.207)	*0.0002, **0.0027
AFP	11.303 (14.929)	9.61 (12.743)	8.973 (11.288)	NS
Ferritin	120.137 (129.5)	132.611 (107.7)	271.294 (327)	**0.0139, ***0.0176
LDL	101.265 (24.85)	111.838 (29.84)	105.606 (24.65)	NS
HDL	58.265 (17.83)	64.486 (17.159)	60.394 (15.532)	NS
TG	110.735 (48.23)	94.243 (36.82)	120.15 (100.27)	NS
HbA1c	5.537 (0.534)	5.708 (0.457)	5.718 (0.595)	NS
BW	52.863 (8.779)	54.115 (8.994)	55.241 (11.112)	NS

HT medication	13	15	12	NS
Statin use	1	2	1	NS
DM medication	2	3	7	NS

The data are presented as mean (standard deviation).

The normal range of clinical parameters in fasting serum was as follows: ALT 5–40 U/L, albumin 3.8–5.2 g/dL, platelet male 13.1–36.2 × 10^4/μL, platelet female 13.0–36.9 × 10^4/μL, LDL 70–139 mg/dL, HDL male 40–86 mg/dL, HDL female 40–96 mg/dL, triglyceride 50–149 mg/dL, creatinine male 0.61–1.04 mg/dL, creatinine female 0.47–0.79 mg/dL, ferritin male 39.4–340 ng/mL, ferritin female 3.6–114 ng/mL and HbA1c 4.6–6.2%. All laboratory data measurements were conducted after overnight fasting. The units of HCV-RNA are log IU/mL. No significant differences were found between the no change and upregulation groups. “*”, “**” and “***”indicate significant differences between DCV/ASV and SOF/LDV, between DCV/ASV and SOF/RIB, and between SOF/LDV and SOF/RIB, respectively.

Table 2. Changes in symptom markers from the start of DAA treatment to 1 year after

PROs	start of DAA	1 year after	p value
CSS total	6.626 (4.27)	5.196 (4.043)	< 0.0001
CSS1	0.252 (0.497)	0.262 (0.555)	NS
CSS2	0.421 (0.583)	0.402 (0.657)	NS
CSS3	0.841 (0.689)	0.579 (0.630)	< 0.0001
CSS4	1 (0.858)	0.679 (0.787)	< 0.0001
CSS5	1.215 (0.727)	1.047 (0.757)	0.0237
CSS6	0.822 (0.867)	0.636 (0.719)	0.0177
CSS7	0.642 (0.771)	0.467 (0.634)	0.0127
CSS8	0.421 (0.533)	0.290 (0.495)	0.0156
CSS9	1.009 (0.759)	0.832 (0.666)	0.0255
K-6	2.701 (3.286)	1.738 (2.869)	0.0018
ESS	3.692 (3.266)	3.243 (2.681)	0.0719
PSQI	7.14 (3.435)	6.664 (2.681)	0.0388

The data are presented as mean (standard deviation).

Table 3. Change in prevalence of sick symptoms from the start of DAA treatment to 1 year after

Sick symptoms	start of DAA	1 year after	p value
Poor sleeper/ESS	6	3	0.0077
Poor sleeper/PSQI	70	60	< 0.0001
MHE/CSS	39	23	< 0.0001
PD/K-6	3	1	0.0280
RLS	13	8	0.0072

“MHE” is minimal hepatic encephalopathy. “PD” is psychological distress.

Table 4. Change in items on the SF-36 from the start of DAA treatment to 1 year after

Items	start of DAA	1 year after	p value
PFN	43.9 (12.8)	41.6 (11.52)	0.0591
RPN	44.3 (12.3)	43.9 (13.2)	NS
BPN	48 (11)	48.3 (10.5)	NS
GHN	45 (9.3)	45 (8.7)	NS
VTN	48.6 (10.6)	48.6 (10.3)	NS
SFN	48.2 (12.6)	48.5 (10.4)	NS
REN	45.6 (12.6)	45 (13.5)	NS
MHN	49.8 (10.3)	49.8 (9.8)	NS
PCS	43.3 (11.6)	42.1 (12.8)	0.0997
MCS	50.7 (9.2)	51.3 (8.8)	NS
RCS	47.5 (12)	47.7 (12.7)	NS

Table 5. Uni- and multivariate analysis for changes in CSS score

A. Deterioration: CSS increases 1 unit or more at 1 year

	Single factor			Multi factors		
Factors	p value	odds	95% CI	p value	odds	95% CI
Non2B	0.0278	0.081	0.009–0.761	0.0275	0.074	0.007–0.749
HT+	0.7055	1.187	0.487-2.896			
LDL0	0.1024	0.986	0.969–1.003			
Male	0.2220	1.722	0.720–4.123			
ESS0	0.9786	0.000	not detect			
RLS1Y	0.0314	5.208	1.159–23.424	0.0188	6.639	1.369–32.204

B. Amelioration: CSS decrease of 3 units or more at 1 year

	Single factor			Multi factors		
Factors	p value	odds	95% CI	p value	odds	95% CI
Non2B	0.4466	2.375	0.256–22.043			
HT−	0.1575	0.558	0.248–1.253	0.0758	0.443	0.180–1.088
LDL0	0.0908	1.014	0.998–1.030			
Male	0.1090	0.493	0.207–1.171			

ESS0	0.0403	9.853	1.107–87.735
RLS1Y	0.1762	0.229	0.027–1.938

The CSS deterioration group had CSS increase 1 unit or more from the start of DAA to 1 year, whereas, a decrease of 3 units or more in CSS is the CSS amelioration group. “Non2B” is 1B or 2A HCV genotype. “HT−” is non-HT drug users. “LDL0” is non-elevated LDL at the start of DAA. “ESS0” is a poor sleeper by ESS at the start of DAA. “RLS1Y” is has RLS at 1 year. CI is confidence interval.

Figure Legends

Figure. Relationship between changes in CSS and clinical factors.

Changes in CSS were calculated by subtracting the CSS score before DAA from the score at 1 year. Change scores of 1 unit or more were defined as the CSS recovery group and the other patients were included in the CSS worsening group. Error bars represent the standard deviation. Differences between the groups were evaluated by a *t*-test, and values of $p < 0.05$ were considered statistically significant. **A**. Hypertension drug users (HT+) were more likely to recover ($p = 0.0699$). The Y axis is changes of CSS (A, C, D, E, F, and G). **B.** The CSS worsening group had a lower value of LDL at the start of DAA ($p = 0.047$). Y-axis is value of serum LDL (mg/dL). **C.** Patients with HCV genotype 2B were more likely to worsen than 1B and 2A ($p = 0.0313$ between 1B and 2B, $p = 0.0321$ between 2A and 2B), **D** but CSS changes did not differ by type of DAA treatment. **E**. Poor sleepers by ESS at the start of DAA had recovery ($p = 0.03$), **F** but those with restless leg syndrome at 1 year worsened ($p = 0.0202$). **G**. Female patients were more likely to recover than male patients ($p = 0.0244$).

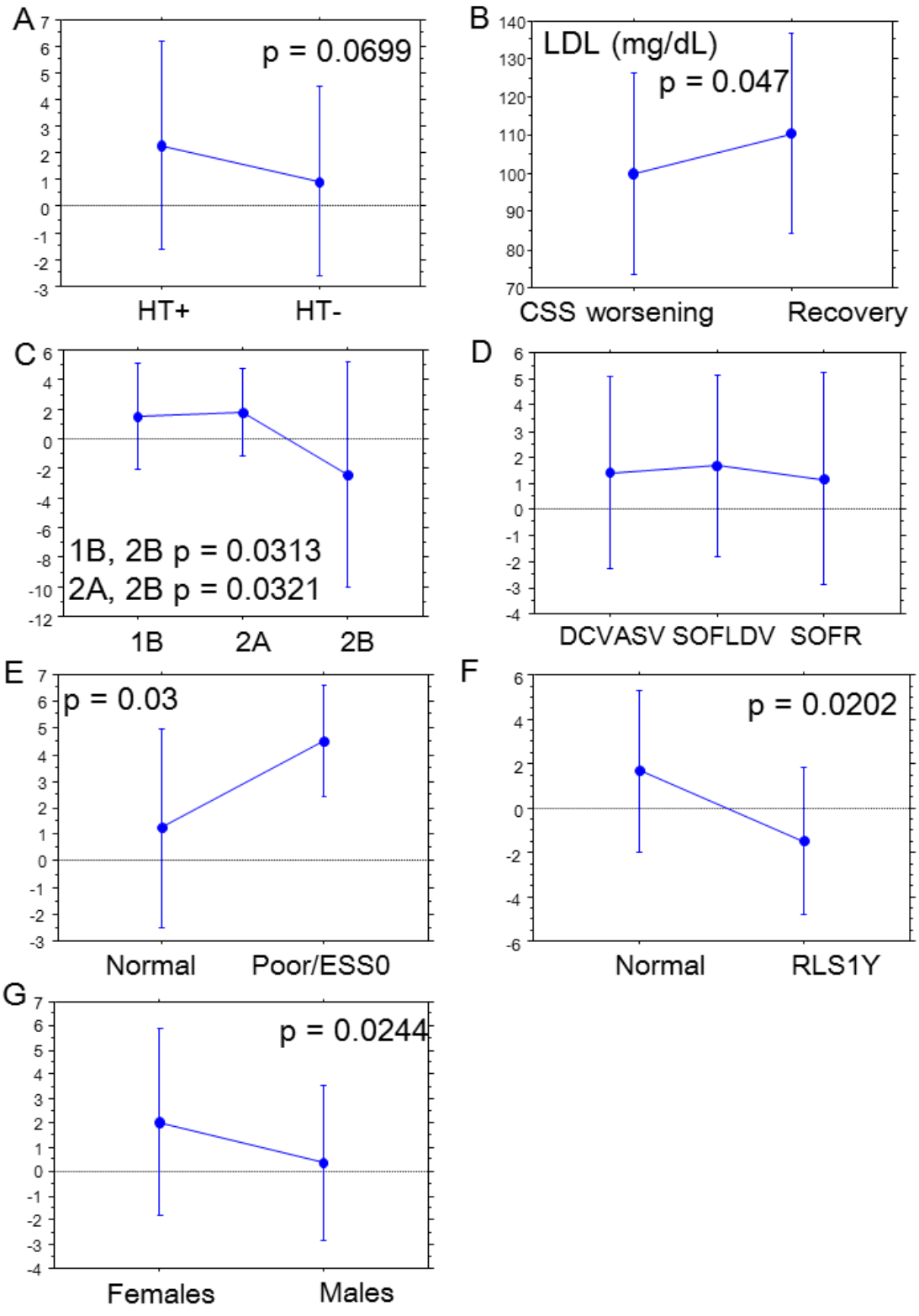

Figure. Ichikawa T. et. al.,