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Prevalence and Incidence of Depression during Interferon-Based Antiviral Therapy in Chronic Hepatitis C Patients in the Republic of Korea

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Background/Aims: The association between depression and chronic hepatitis C virus (HCV) infection or pegylated interferon α and ribavirin therapy (PR therapy) has not been extensively studied in Korea. We aimed to clarify the prevalence of depression and its incidence during PR therapy in chronic hepatitis C (CHC) patients. **Methods:** In this prospective, multicenter study, 114 CHC patients were screened for depression using two self-reported scales, the Beck Depression Inventory-I (BDI-I) and the Hospital Anxiety and Depression scale (HADS). The incidence of depression during PR therapy was evaluated in 62 patients who underwent PR therapy during the study period. **Results:** The prevalence of baseline depression was 17.5% according to the BDI-I score ≥10 criterion and 4.4% according to the HADS-D score ≥8 criterion in the 114 CHC patients, and it was significantly associated with an unmarried state. During PR therapy, depression developed in 34.6% according to the BDI-I scale and 29.5% according to the HADS-D, which negatively affected sustained virologic response (SVR). **Conclusions:** The prevalence of depression in Korean CHC patients appears to be low compared to that in Western patients; however, its incidence during PR therapy (approximately 30%) was similar to that of other populations, which led to a lower SVR rate. Active screening and multidisciplinary management of depression during PR therapy is warranted. **(Gut Liver 2017;11:426-433)**

Key Words: Hepacivirus; Depression; Interferons; Beck Depression Inventory-I; Hospital Anxiety and Depression scale

INTRODUCTION

Hepatitis C virus (HCV) infection is a global health problem that affects about 185 million people with an estimated prevalence of 2.8%.[1] Not only increasing mortality and morbidity of HCV-related advanced liver diseases, but also patient-reported outcomes, including quality of life or mental health status lead to a significant global disease burden.

Previous studies in Western countries showed that patients with chronic HCV infection were associated with high prevalence of psychiatric and neurologic abnormalities. Moreover, pegylated interferon α and ribavirin therapy (PR therapy) can induce depression so that uncontrolled pretreatment depression is a major contraindication of PR therapy in chronic hepatitis C (CHC) patients.[2,3] Although direct acting antivirals are applied to CHC patients, PR therapy is still widely used in many Asian countries and resource-limited regions.[4]

The epidemiology and risk factors of HCV infection as well as sociocultural background related to mental health status vary in different global regions. For example, intravenous drug use (IVDU), which is closely related to psychiatric abnormalities *per se*, is the major risk factor for HCV infection in Western countries,[5-7] whereas it is only a minor risk factor in South Korea.[8,9] Because there was few data on depression in Korean CHC patients, this study aimed to prospectively evaluate the prevalence of depression and its incidence during PR therapy.

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MATERIALS AND METHODS

1. Patients

From July 2011 to September 2014, 114 patients with chronic HCV infection were prospectively enrolled in three university hospitals (Seoul National University Bundang Hospital [SNUBH], Chonbuk National University Hospital [CNUH], and Soonchunhyang University Bucheon Hospital [SUBH]). The prevalence of depression was assessed in the 114 patients, who were treatment naïve (n=65) or had failed previous treatment (n=49). Patients with hepatitis B virus or human immunodeficiency virus coinfection and those who received antiviral therapy other than PR therapy such as first generation protease inhibitors in clinical trial setting, were excluded from this study.

Among the 114 patients, 62 patients began PR therapy during the study period, and underwent serial evaluation of depressive symptoms during PR therapy. In 62 patients, baseline depression before PR therapy was found in 10 patients by the Beck Depression Inventory-I (BDI-I) scale, and one patient by the Hospital Anxiety and Depression Scale (HADS). Therefore, the incidence of depression during PR therapy was evaluated separately in the 52 patients by the BDI scale and 61 patients by the HADS-D.

Informed written consent was obtained from all participants after approval of the study protocol by the Institutional Review Boards of the three hospitals (B-1109-1136-008, SNUBH; 2012-02-015-009, CNUH; and 2011-1-093, SUBH), and this study was carried out in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Helsinki Declaration in 1997 (revised in 2000).

2. Screening of depression

For screening of depression, two kinds of validated self-assessment scales, the BDI-I and the HADS, were used for each patient.

BDI-I is a 21-item measure in which items are rated on a 0 to 3 scale and summed for a total score of 0 to 63. Higher scores indicate a greater degree of depressive symptoms.[10,11] The standardized range of BDI-I score adopted by Shin *et al*.[12] for minimal depression was 0 to 9; mild depression, 10 to 15; moderate depression, 16 to 23, and severe depression, 24 to 63.

HADS consists of 14 items measuring depression and anxiety. It is divided into an anxiety subscale (HADS-A) and a depression subscale (HADS-D), and it omits the somatic symptoms of depression and anxiety which are frequently present in medically ill patients. Using the most commonly used cutoff score of 8, minimal depression was defined as a HADS score of 0 to 7, mild as 8 to 10, and moderate to severe depression as 11 to 21.[13]

If severe depression developed according to either of the above 2 scales, antidepressants were prescribed or the patients were referred to psychiatrists. Separately from the depression scales, the other standardized questionnaire survey was carried out in each patient with the assistance of the research coordinators. The questionnaire included data on patient demographics (e.g., age, gender, and marital status), potential risk factors for HCV infection, use of alcohol and other psychoactive substances, current or past treatment for depression, past history of PR therapy for chronic HCV infection, and laboratory results.

3. Statistical analysis

Continuous variables were expressed as means±standard deviation, and continuous variables were compared by an independent t-test or nonparametric Mann-Whitney U-test. Categorical data were compared with the chi-square test or Fisher exact test. The cumulative incidence of depression during PR therapy was analyzed using the Kaplan-Meier method. A p-value of <0.05 was considered to indicate a statistically significant difference. Data were analyzed using SPSS for Windows version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Patients characteristics

The clinical characteristics of the 114 subjects are summarized in Table 1, showing the mean age to be 54.7 years with a male gender in 55.3%. They included 86 patients (75.4%) with chronic hepatitis, 23 patients (20.2%) with liver cirrhosis, and five patients (4.4%) with hepatocellular carcinoma (HCC). In the cirrhosis and HCC patients, Child-Pugh class A and B were (92.9%) and (7.1%), respectively. Among them, only three patients (2.6%) were past IVDUs, and four patients (3.5%) had a past history of depression.

2. The prevalence of baseline depression and its related factors in chronic HCV infected patients

In the 114 patients, the prevalence of baseline depression was 17.5% (n=20) defined as BDI-I $\geq$10, while it was 4.4% defined as HADS-D $\geq$8. The prevalence of baseline depression according to the different cutoff levels of either BDI-I scale or HADS are summarized in Table 2. It shows that the prevalence of moderate to severe depression by BDI $\geq$16 was 7.9% with a higher rate in women than in men. However, by the HADS, anxiety was more prevalent than depression. The comparative features of the depressive patients (BDI-I $\geq$10) and not-depressive patients (BDI-I $<$10) at enrollment are presented in Table 3, showing the unmarried state was significantly more common in depressive patients, while age, gender, education level, liver disease state, HCV genotype or other laboratory results were not different between the two groups. The prevalence of depression among chronic hepatitis, liver cirrhosis, and HCC subgroup was not significantly different.

3. The incidence of depression during PR therapy

After enrollment, the 62 patients who underwent PR therapy were serially evaluated by depressive screening during anti-

Table 1. Baseline Characteristics of 114 Korean Patients with Chronic Hepatitis C Virus Infection

Variable	Value
Age, yr	54.7±1.1
Male sex	63 (55.3)
BMI, kg/m^2	23.7±0.3
>25	34 (29.8)
Education, ≥high school (n=108)	71 (62.3)
Marital status, married (n=111)	103 (90.4)
Current or former alcohol intake (n=113)	66 (57.9)
Current or former smoking	55 (48.2)
Past history of intravenous drug use (n=112)	3 (2.6)
Liver disease diagnosis	
Chronic hepatitis	86 (75.4)
Liver cirrhosis	23 (20.2)
Hepatocellular carcinoma	5 (4.4)
Laboratory results	
WBC, mm^3	4,936.6±176.6
Hemoglobin, g/dL	13.8±0.2
Platelet, ×1,000/mm^3	163.0 ±5.8
Albumin, g/dL	4.2±0.3
Total bilirubin, mg/dL	1.0±0.4
AST/ALT, IU/L	65.8±4.5/69.7±6.1
Prothrombin time, INR	1.1±0.1
Creatinine, mg/dL	1.0±0.2
HCV RNA level, $\log_{10}$ IU/mL (n=105)	5.43±1.33
HCV genotype 1/non-1 (n=99)	42 (42.4)/57 (57.6)
History of past antiviral treatment*	49 (43.0)
History of depression	4 (3.5)

Data are presented as mean±SD or number (%).
BMI, body mass index; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; HCV, hepatitis C virus.
*Forty-nine patients did not achieve sustained virological response after previous pegylated interferon α and ribavirin combination therapy, and the remaining 65 patients did not undergo antiviral therapy.

viral therapy. Among them, 52 patients were depression-free at pretreatment by the BDI-I scale, in whom depression (BDI-I score ≥10) developed in 18 patients (34.6%) during PR therapy. However, 61 patients were depression-free at pretreatment by the HADS-D, and of these 18 patients (29.5%) developed depression during PR therapy. The changes of depression score for those patients who developed depression over the course of PR therapy in both BDI-I scale and HADS-D are presented in Fig. 1. The overall cumulative probability of depression development by BDI-I ≥10 during antiviral therapy was 21.5% at 12 weeks and 38.3% at 36 weeks of treatment, while the cumulative probability using HADS-D ≥8 was 21.5% at 12 weeks and 34.2% at 36 weeks of PR therapy (Fig. 2).

The patients who developed depression (BDI-I ≥10) during PR therapy showed a significantly lower sustained virologic response (SVR) rate (55.6%, 10/18) than 85.3% (29/34) than in the patients who did not develop depression (Table 4). Though the treatment discontinuation rate was higher in depression-developed patients (5/18), only one of the five patients discontinued due to depression, and the other four discontinued due to hematologic adverse events (n=1), fatigue (n=1), no early virologic response at 12 weeks of PR therapy (n=2).

Among 10 patients who had pretreatment depression (BDI-I score ≥10), three patients showed aggravation of depression, four patients remained in a stationary depression state, and the remaining three showed decreased BDI scores of <10 during PR therapy (Fig. 3). Antidepressive therapy was prescribed to two patients showing aggravated depression symptoms with BDI-I scores of 27 and 25, respectively, which recovered after PR therapy. Among seven patients who were evaluated after PR therapy, six recovered from depression while one patient remained at a posttreatment BDI-I score of 11.

DISCUSSION

This prospective, multicenter study demonstrated that the prevalence of depression was 17.1% by BDI-I ≥10 or 4.4% by

Table 2. Prevalence of Depression in 114 Patients with Chronic Hepatitis C Virus Infection According to the BDI-I and HADS

Depression screening tool and cutoff	Total (n=114)	Male (n=64)	Female (n=50)
Depression defined as BDI-I score ≥10	20 (17.5)	10 (15.9)	10 (19.6)
Mild (BDI score, 10–15)	11 (9.6)	7 (11.1)	4 (7.8)
Moderate (BDI score, 16–23)	8 (7.0)	2 (3.2)	6 (11.8)
Severe (BDI score >23)	1 (0.9)	1 (1.6)	-
Depression defined as HRDS-D ≥8	5 (4.4)	3 (4.8)	2 (3.9)
HADS-A score ≥8	11 (9.6)	5 (7.9)	6 (11.8)
HADS-T score ≥16	5 (4.4)	3 (4.8)	2 (3.9)

Data are presented as number (%).
BDI-I, Beck Depression Inventory-I; HADS, Hospital Anxiety and Depression scale; HADS-D, HADS-Depression; HADS-A, HADS-Anxiety; HADS-T, HADS-Total.

Table 3. Comparison of Clinical Variables between Patients with a Positive Screen for Depression (BDI-I ≥10) and Patients with BDI-I <10

Variable	Depressive patients (BDI-I ≥10, n=20)	Not-depressive patients (BDI-I <10, n=94)	p-value
Age, yr	55.1±14.1	54.7±10.6	0.811
Male sex	10 (50.0)	53 (56.4)	0.628
BMI, kg/m^2	22.7±1.9	23.9±3.1	0.113
>25	3 (15.0)	31 (33.0)	0.177
Education, ≥high school	11 (57.9)	60 (67.4)	0.436
Marital status, married	15 (78.9)	88 (95.7)	0.028
Current or former alcohol intake	13 (65.0)	53 (57.0)	0.620
Current or former smoking	10 (50.0)	45 (47.9)	1.000
History of intravenous drug use	2 (10.0)	1(1.1)	0.082
Past history of depression	2 (10.0)	2 (2.1)	0.141
Chronic hepatitis in diagnosis	14 (70.0)	72 (76.6)	0.571
HCV genotype 1	11 (61.1)	46 (56.8)	0.797
Previous antiviral treatment	9 (41.5)	38 (45.0)	0.807
WBC, mm^3	4,802.1±1,896.1	4,965.8±1,872.7	0.750
Hemoglobin, g/dL	13.2±1.7	13.9±1.8	0.135
Platelet, ×1,000/mm^3	157.6±68.3	164.2±59.8	0.624
Prothrombin time, INR	1.1±1.2	1.1±1.1	0.799
Albumin, g/dL	4.2±0.5	4.2±0.3	0.672
Total bilirubin, mg/dL	0.96±0.4	0.96±0.4	0.964
Creatinine, mg/dL	1.1±0.6	1.1±1.8	0.623
HCV RNA, $\log_{10}$ IU/mL	5.68±1.17	5.37±1.37	0.432
AST, IU/L	63.4±33.1	66.3±51.0	0.646
ALT, IU/L	81.8±84.1	67.1±60.2	0.235

Data are presented as mean±SD or number (%).
BDI-I, Beck Depression Inventory-I; BMI, body mass index; HCV, hepatitis C virus; WBC, white blood cell; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

HADS-D in chronic HCV-infected Korean patients, in whom a history of IVDU was only 2.5%, and baseline depression was related to an unmarried state. During PR therapy, 34.6% and 29.5% of depression-free patients at pretreatment developed depression, by BDI-I ≥10 and by HADS-D, respectively. Those who develop depression showed a significantly lower SVR rate and higher discontinuation of PR therapy than those who did not develop depression. Only two patients required antidepressant therapy during PR therapy and most of them recovered from depression after therapy, while one had persistent depression 6 months after the completion of PR therapy.

According to the Korea National Health & Nutrition Examination Survey 2014 using Patient Health Questionnaire 9 (PHQ-9) ≥10, the prevalence of depression in the general population of Korea was 8.8% in women and 4.3% in men (≥19 years old). In our study, the prevalence rate of depression by BDI-I in CHC patients was 19.2% in women and 15.5% in men, which seems to be higher than in general population of Korea, especially in men, though different screening tools and population characteristics did not permit direct comparison.

The prevalence of depression in chronic HCV-infected patients has been reported as 29.7% in a large American cohort (n=4,781) with a history of IVDU in 51.4% showing higher prevalence than the approximately 9% in general population using PHQ-8 (PHQ-8) with a cutoff score ≥10,[7] which was similar to the other study results.[5,14] According to the data from the National Health and Nutrition Examination Survey (2005 to 2010, n=10,231), CHC was independently associated with depression, while chronic hepatitis B was not, in which depression prevalence by PHQ-9 in HCV patients was 54.6% including major depressive disorder in 11.4%.[5,15-18] In Australian CHC patients (n=395), depression prevalence by HADS-D ≥8 was 27%, which was 2.4 times higher than community norms and was related to an unmarried state.[6] In a Japanese national survey, patient-reported depression rate was 7.1%. However, data from Asian countries on the prevalence of depression in CHC patients are scarce, while a high prevalence (51.6%) of depression by BDI-II was reported in 67 Chinese IVDUs.[19]

The depression prevalence in our patients seemed to be lower than in Western countries. Though the reason is not clear, the

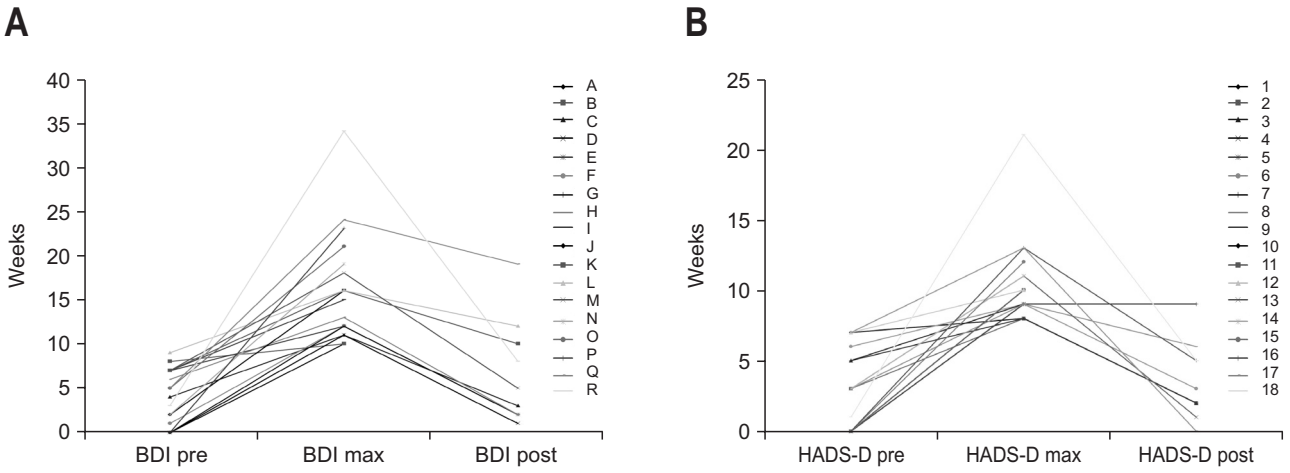
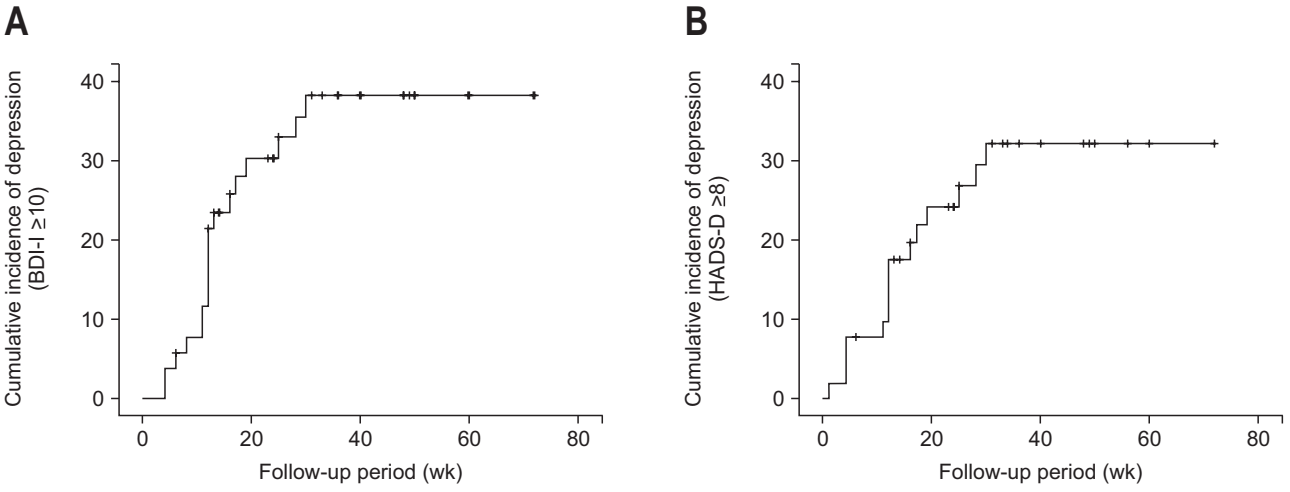


Fig. 1. Development of depression during antiviral treatment. Depressive symptoms developed in 34.6% (n=18) with a BDI-I score ≥10 (A) and 29.5% (n=18) with a HADS-D score ≥8 (B) among 52 and 61 patients who had no depression at baseline, respectively. The point prevalence of moderate to severe depression (BDI-I score ≥16 and HADS-D ≥11) was 17.3% (n=9) according to the BDI-I score and 9.8% (n=6) according to the HADS-D score over the course of pegylated interferon and RBV therapy. The majority of patients exhibited increased BDI-I or HADS-D scores during treatment, which returned to normal after the completion of treatment.
BDI-I, Beck Depression Inventory-I; HADS-D, Hospital Anxiety and Depression scale-Depression.



FU period	0	12	24	36
No. of Pt. at risk	52	40	30	23
%	0	21.5	30.4	38.3

FU period	0	12	24	36
No. of Pt. at risk	61	47	38	28
%	0	21.5	27.2	34.2

Fig. 2. Cumulative incidence of depression during antiviral treatment with pegylated interferon α and ribavirin. The cumulative incidence rates of depression during antiviral therapy were 21.5% versus 21.5% at 12 weeks, 30.4% versus 27.2% at 24 weeks, 38.3% versus 34.2% at 36 weeks according to BDI-I (A) versus HADS-D (B), respectively.
BDI-I, Beck Depression Inventory-I; HADS-D, Hospital Anxiety and Depression scale-Depression; FU, follow-up; Pt., patients.

different epidemiology and patient's characteristics may be the reason, especially IVDU experience was very low (only 3%) in our subjects, revealing a marked difference from Western patients. IVDU was highly associated with depression or other psychiatric problems.

Our patients with pretreatment depression showed a higher rate of unmarried state, reflecting marital function as a social support, which was compatible with a previous study.[15] Because the major risk factor for HCV infection in Korea was health-care related rather than IVDU, this may be related to the predictor of depression as well as prevalence of depression.

In this study, 34.6% by BDI-I or 29.5% by HADS-D of depression-free patients at pretreatment developed depression during PR therapy. An Asian study in Japan[20] using the BDI-II reported that the incidence of depression during PR therapy increased from 0% at baseline to 21% at 4 weeks and 34% at 12 weeks

Table 4. Comparison of Clinical Variables between Patients Who Developed (BDI-I ≥10) and Did Not Develop (BDI-I <10) Depression during Pegylated Interferon and Ribavirin Therapy (n=52)

Variable	Depression (BDI-I ≥10, n=18)	No depression (BDI-I <10, n=34)	p-value
Age, yr	51.89±9.0	53.74±9.5	0.532
Male sex	9 (50.0)	24 (70.6)	0.226
BMI, kg/m^2	25.0±4.0	24.0±2.9	0.269
≥25	9 (50.0)	12 (35.3)	0.309
Education, ≥high school	14 (82.4)	22 (66.7)	0.247
Marital status, married	17 (100.0)	31 (93.9)	0.305
Current or former alcohol intake	12 (66.7)	21 (63.6)	0.830
Current or former smoking	12 (66.7)	16 (47.1)	0.245
Intravenous drug user, yes	0	0	-
Past history of depression, yes	0	0	-
Chronic hepatitis in diagnosis	16 (88.9)	23 (67.6)	0.096
HCV genotype 1	7 (38.9)	10 (33.3)	0.700
Previous antiviral treatment	12 (66.7)	22 (64.7)	0.889
WBC, mm^3	4,597.8±1,440.2	4,902.4±2,037.1	0.908
Hemoglobin, g/dL	13.5±1.5	14.1±1.8	0.317
Platelet, ×1,000/mm^3	167.752±56.954	174.9±65.6	0.878
Prothrombin time, INR	1.03±0.10	1.06±0.08	0.353
Albumin, g/dL	4.3±0.4	4.2±0.4	0.658
Total bilirubin, mg/dL	0.9±0.3	1.0±0.4	1.000
Creatinine, mg/dL	0.8±0.3	0.8±0.2	0.353
HCV RNA level, log$_{10}$ IU/mL, (3/29)	4.84±0.98	5.23±1.48	0.144
AST, IU/L	60.82±53.85	59.68±45.92	0.944
ALT, IU/L	67.24±85.71	60.24±38.62	0.280
SVR	10 (55.6)	29 (85.3)	0.020
Treatment discontinuation	5 (27.8)	1 (2.9)	0.008
Depression as the reason of treatment discontinuation	1 (20.0)	0	0.655
Post treatment BDI-I score, ≥10	3 (30.0)	0	0.008

Data are presented as mean±SD or number (%).
BDI-I, Beck Depression Inventory-I; BMI, body mass index; HCV, hepatitis C virus; WBC, white blood cell; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SVR, sustained virologic response.

of PR therapy, which is quite similar to our study results. These depression incidences throughout PR therapy seem to resemble results from many preceding studies in other countries, e.g., 35% to 55.7% (USA)[5,15,16] 27% (Austria),[6] 36.7% to 41% (Italy),[21,22] 20% to 44% (Japan),[20,23] and 28% (India).[24] The depression development group in this study showed a significantly lower treatment completion rate and lower SVR rate.

Predictors for the development of depression during PR therapy in previous studies were a history of depression, low social support, history of alcohol usage, history of intravenous drug usage, history of major depression and ribavirin dosage assignment.[7,15,25-28] However, we did not find any significant variables related to development of depression, probably because of small sample size and different subject characteristics.

We used two scales for the screening of depression (BDI-I score and HADS-D score), and baseline depression prevalence was not concordant between the two scales: 17.6% versus 4.3% measured by BDI-I score and HADS-D score, respectively. If the BDI-I cutoff level were set at 16 rather than 10, the moderate to severe depression rate was 7.6%, which was similar to the 4.3% of the HADS-D for depression. The BDI scale is frequently used in studies on depression in medical illness including HCV, but it contains several somatic symptoms of chronic illness such as fatigue, sleep difficulty and appetite changes, therefore, false positive detection of depression could occur, despite the high sensitivity and high negative predictive value.[25,29] In contrast, HADS was developed to exclude both somatic components and serious mental symptoms which were less common in patients attending non-psychiatric clinics. The sensitivity and specificity for both HADS-A and HADS-D were approximately 0.8.

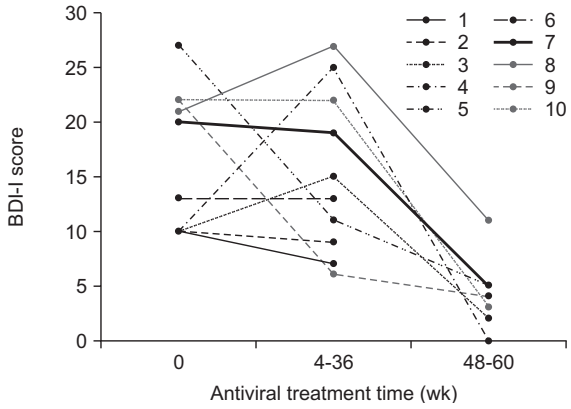


Fig. 3. Changes in the Beck Depression Inventory-I (BDI-I) score during pegylated interferon and ribavirin therapy among patients with underlying depression at baseline. Seven patients with pretreatment depression showed aggravation of the BDI-I score during antiviral therapy, and two patients (number 2 and number 10) received antidepressant therapy. Moreover, one patient did not recover after 6 months from the end of pegylated interferon α and ribavirin therapy.

The correlation coefficients between the HADS and BDI were reported as 0.62 to 0.73, which was concordant with our study results (the Spearman's rank correlation coefficient between the BDI-I score and the HADS-D score was 0.66, data not shown).[13]

This study has some limitations. First, it was based on self-reported surveys which could be biased with lack of more stringent psychiatric exclusion criteria for depression. However, such surveys remain the practical way to evaluate patient-reported outcomes. Second, though the subjects were enrolled in three hospitals, the sample size is relatively small, and external validation may be required to represent overall Korean patients. Third, not all patients responded to the survey at the planned time points.

In conclusion, the prevalence of depression in Korean CHC patients seems to be low compared to Western patients, however, the incidence of depression during PR therapy (about 30%) was similar to that of other populations, which led to a lower SVR rate. Active screening and multidisciplinary management of depression in CHC patients during interferon-based therapy is warranted, which will be overcome by direct acting antiviral therapy in near future.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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