Direct-acting antiviral treatment is safe and effective for chronic HCV patients with psychiatric disorders

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Abstract. Although most patients with hepatitis C virus (HCV) infection have been cured since the introduction of direct-acting antiviral (DAA) treatments, whether patients with psychiatric disorders and chronic HCV infection receive benefits from DAA treatments remain unclear. The efficacy and safety of DAA treatment were compared between patients with and without psychiatric disorders. Data were retrospectively collected from medical records at the Suzuka General Hospital (Japan) between September 2014 and December 2021. The study was an observational, single-center study. Fisher's exact test, Mann-Whitney U test and Friedman's test were used for the comparisons between groups. Patients with HCV infection who had been started on DAA treatments were included. In total, 15 HCV cases with psychiatric disorders (P) and 209 HCV cases with nonpsychiatric disorders (NP) were started on DAA treatments for HCV infection. Patients in group P were younger (55±13.9 years) compared with those in group NP (68±13.0 years). A total of 12 patients (80%) in group P achieved and 188 patients (90%) in group NP achieved sustained virologic response (SVR), with no significant difference between the two groups. The remaining three patients in group P who did not achieve SVR included two drop-out cases. Regarding the laboratory data at the end of DAA treatments and SVR, there were no significant differences between the two groups. There were no cases of discontinuation or reduction of medication due to psychiatric disorders during DAA treatment. DAA treatment for HCV infection is effective, tolerable and safe for psychiatric patients, as well as patients without psychiatric disorders. Psychiatric patients with HCV infection should undergo DAA treatment to prevent progression to liver failure and/or cancer.

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Introduction

Almost all cases of HCV infection have been cured since the worldwide introduction of direct-acting antivirals (DAAs), including Japan (1-7), and sustained virologic response (SVR) induced by DAA treatment for HCV results in significantly lower all-cause mortality and lower incidence rates of hepatocellular carcinoma (HCC) (8). Though marked improvements in the treatment and prognosis of patients with HCV infection have been achieved, certain patient populations, for example, those having a serious underlying disease, have not received the benefits of the advancements made in HCV treatment. Patients with psychiatric disorders are one such population. Unfortunately, they have been excluded from antiviral treatment with interferon-based regimens because of their neuropsychiatric side effects, insufficient treatment compliance or, more likely, due to re-infection from their continued intravenous drug use (9-12). In the era of interferon-based regimen treatment, only a few patients with psychiatric disorders were treated successfully and achieved SVR (9). Although psychiatric disorders may inhibit to starting treatment for HCV-infected patients, it is necessary to treat HCV infection in patients with psychiatric disorders, because HCV infection itself was associated with psychiatric disorders (13-15) and psychiatric disorders are common co-morbidities of individuals with HCV infections (9). DAA treatment is more effective and tolerated than interferon-based treatment for HCV infection. Therefore, DAA treatment for patients with psychiatric disorders has to be considered to decrease HCV infection in this vulnerable population and achieve HCV eradication for everyone, including vulnerable individuals. To the best of our knowledge, although there are limited reports on DAA treatment in patients with HCV and psychiatric disorders in Europe and the United States (16-18), none were reported in Asia, especially Japan.

In the current study, data were analyzed and compared between patients from patients with HCV treated with DAAs who presented or did not present psychiatric disorders. The efficacy and safety of DAA treatment for patients with psychiatric disorders were also examined.

Patients and methods

Patients. This was an observational, single-center study in which data were retrospectively collected from the medical records of Suzuka General Hospital (Japan) between September 2014 and December 2021. Patients with HCV infection who had been started on DAA treatment for their HCV infection at the Department of Gastroenterology of the hospital were included. In total, 15 (7 males and 8 females) and 209 (110 males and 99 females) patients with HCV and psychiatric disorders (P) or with non-psychiatric disorders (NP), respectively, were started on DAA treatment for HCV infection. The 15 cases of HCV in Group P included 2 cases with chronic hepatitis after acute HCV infection (19), and, of the 209 cases of HCV cases in Group NP, 1 had chronic hepatitis after acute HCV infection. Oral informed consent, including a statement of agreement to the use of their samples in scientific research, was obtained from each patient at the first medical examination in the Outpatient Department of Suzuka General Hospital (http://www.miekosei.or.jp/2_sch/privacy.html). Informed consent was also obtained in the form of an opt-out on the website. The present study was approved by the Ethics Committee of Suzuka General Hospital (approval no. 284).

Diagnosis. HCV infection was diagnosed based on a patient being positive for both anti-HCV antibody (HCV-Ab) and HCV RNA. Chronic hepatitis infection, cirrhosis and HCC were diagnosed using ultrasonography [Aloka Arietta 850 (Hitachi, Ltd.), Aplio a550 (Canon Medical Systems Corporation Co., Ltd.)], CT (Aquilion TSX-101A and Aquilion PRIME (Canon Medical Systems Corporation Co., Ltd.)] and/or MRI scan [Ingenia Elition 3.0T and Achieva 1.5T (Koninklijke Philips N.V.)]. Serum HCV-Ab levels were measured using a chemiluminescent enzyme immunoassay (cobas e801, cat. no. 30916; Roche Diagnostics). Blood specimens were obtained by drawing blood from each patient, and the serum fraction was obtained by centrifugation (2,100 x g at room temperature for 5 min) of the blood specimens for HCV-Ab level analysis. Measurements of α-fetoprotein (AFP), protein induced by vitamin K absence or antagonist-II (PIVKAII), HCV RNA, serogroup and genotype analyses were performed at LSI Medience Corporation. HCV genotyping was performed when the HCV serotype could not be determined. The detection of HCV amino acid substitutions was performed at SRL, Inc. or the Division of Virology, Department of Infection and Immunity, Jichi Medical University School of Medicine (Tochigi, Japan). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (T-Bil), albumin (Alb) and creatinine (Crea) levels were measured using the Cobas® 8000 modular analyzer series (Roche Diagnosis K.K.) or the Labospect 008 (Hitachi High-Technology Corporation). ALP levels were measured using the Japan Society of Clinical Chemistry (JSCC) method (20). The platelet count was measured using the Sysmex® XE2100I™ hematology automated analyzer (Sysmex Corporation). The prothrombin time (PT) values were measured using the Sysmex CS-2500 automated coagulation analyzer (Sysmex Corporation). Blood samples were obtained from each patient. The serum fraction obtained via centrifugation (2,100 x g at room temperature for 5 min) of the blood specimens were used for the analysis of AST, ALT, ALP, T-Bil, Alb and Crea serum levels. Whole blood samples were used for the platelet count analysis. The plasma that was separated using a blood-collecting container with sodium citrate was used for the analysis of the PT.

Table I. List of psychiatric disorders in hepatitis virus C RNA-positive patients with psychiatric disorders.

Psychiatric disorder	Number of cases
Alcoholism	1
Cenesthopathy	1
Dementia	1
Delirium	1
Depression	7
Dissociative disorder	1
Epileptic psychosis	1
Insomnia	6
Panic disorder	1
Schizophrenia	2
Stimulant psychosis	1

Statistical analysis. Statistical analysis was performed using BellCurve v3.20 (Social Survey Research Information Co., Ltd.) for Excel (Microsoft Corporation). Fisher's exact test, Mann-Whitney U test and Friedman's test were used for the comparisons between groups. These methods of analysis were performed one time for each comparison.

Results

Characteristics of HCV patients with and without psychiatric disorders. Of the 209 patients in the group NP, nine were re-treated after post-DAA treatment relapse or because did not respond to DAA treatment; eight cases were retreated once, while one case was retreated twice using other DAA agents. No cases of HCV/other virus co-infection were found. The co-morbid psychiatric disorders are listed in Table I.

All 15 cases in group P had at least one psychiatric disease, as shown in Table I. The drugs prescribed for these cases were alprazolam, aripiprazole, brotizolam, carbamazepine, chlorpromazine, donepezil, duloxetine, ethyl loflazepate, etizolam, flunitrazepam, haloperidol, levetiracetam, lorazepam, milnacipran, mirtazapine, nitrazepam, olanzapine, sodium valproate, sulpiride and/or zolpidem.

The details of the characteristics before DAA treatment of both groups are presented in Fig. 1. Group P was younger than group NP (55±13.9 years vs. 68±13.0 years, respectively; P=0.04). However, no significant differences in the male/female ratio, history of interferon therapy, chronic hepatitis/cirrhosis ratio, DAA re-treatment and laboratory data were observed between the two groups. Cirrhosis was present in 3 patients (20%) in group P and 43 (20.6%) in group NP (P>0.999).

Amino acid substitutions, DAA treatment initiation and rate of completion of planned DAA treatment. Of the 144 genotype 1 cases, 117 were analyzed for nonstructural protein (NS)4A

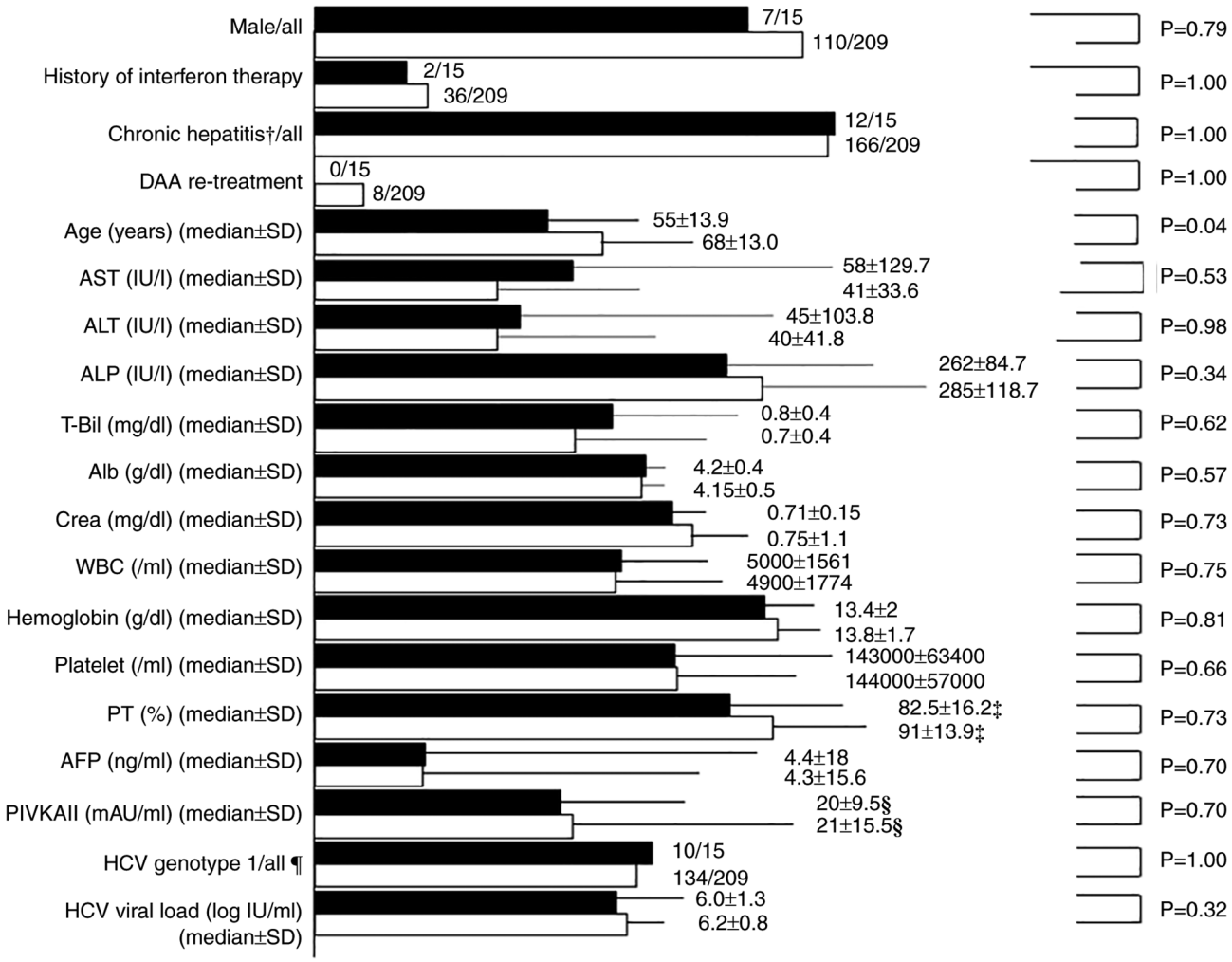

Figure 1. Characteristics of pre-direct-acting antiviral treatment in the P and NP group. The black column indicates the P group and the white column indicates the NP group. †Chronic cases after the acute hepatitis Course were included in chronic hepatitis Cases. ‡Exclusion of anticoagulant therapy cases. §Exclusion of warfarin therapy cases. Genotype1 includes serotype1, genotype1a, and genotype1b and genotype2 includes serotype2, genotype2a and genotype2b. Genotypes other than type 1 and 2 were not detected in the patients. DDA, direct-acting antiviral; P, psychiatric disorder; NP, nonpsychiatric disorder; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; T-Bil, total bilirubin; Alb, albumin; Crea, cotinine; WBC, white blood cells; PT, prothrombin time; AFP, α-fetoprotein; PIVKAII, protein-induced vitamin K absence or antagonist-II; hepatitis C virus.

and NS5A amino acid substitutions before treatment with asunaprevir (ASV) + daclatasvir (DCV), ombitasvir (OBV) + paritaprevir (PTV) + ritonavir (R), ledipasvir (LDV) + sofosbuvir (SOF), or daclatasvir (DCV) + asunaprevir (ASV) + beclabuvir (BCV). Of these 117 cases, HCV amino acid substitutions were detected in 21, as follows: 17 cases of Y93 in NS5A, two cases of L31 in NS5A and two cases of Q80 in NS4A. One of the Q80 in NS4A cases was detected in an HCV RNA genotype 1a case (group NP). A total of two cases who had not had any amino acid substitutions before their first DAA treatment were found to have amino acid substitutions (Y93 or L31) after relapse to the first DAA treatment with ASV + DCV. All cases with Y93 substitutions in NS5A, except for one case in group P, were treated with LDV + SOF. The two cases with amino acid substitutions (Y93 or L31) after relapse to the first DAA treatment with ASV + DCV belonged to the group NP and were re-treated by DCV + ASV + BCV.

The distribution of DAA treatments for the group P was as follows: Four cases of ASV + DCV; three cases of OBV + PTV + R; four cases of SOF + ribavirin (RBV); 1 case of LDV + SOF; and 3 cases of glecaprevir (GLE) + pibrentasvir (PIB). The distribution of DAA treatments for the group NP was as follows: 58 cases of ASV + DCV; 12 cases of OBV + PTV + R; 44 cases of SOF + RBV; 42 cases of LDV + SOF; 45 cases of GLE + PIB two cases of DCV + ASV + BCV; three cases of elbasvir (EBV) + grazoprevir (GZR); two cases of SOF + velpatasvir (VEL); and one case of SOF + VEL + RBV (Table II). The planned dosage period of each DAA treatment was as follows: ASV + DCV for 24 weeks, OBV + PTV + R for 12 weeks, SOF + RBV for 12 weeks, LDV + SOF 12 for weeks, EBV + GZR for 12 weeks, GLE + PIB for 8 or 12 weeks, DCV + ASV + BCV for 12 weeks, SOF + VEL for 12 weeks and SOF + VEL + RBV for 24 weeks. Concerning treatment with GLE + PIB, cases without cirrhosis were treated for 8 weeks, while cases with cirrhosis were treated for 12 weeks. Of the 15 cases in group P, three patients had incomplete treatment because of T-Bil elevation (one case, 1 week of treatment), aggravation of daily living activities (one case, 4 weeks of treatment) and treatment discontinuation requested by the patient (one case, 18 weeks of treatment). Of the 209 cases in the group NP, 13 had

Table II. DAA treatment for hepatitis virus C infection for patients in the P and NP groups.

DAA treatment	Group P, n	Group NP, n	Total, n
ASV/DCV	4	58	62
Ombitasvir/paritaprevir/ritonavir	3	12	15
Ledipasvir/SOF	1	42	43
SOF/RBV	4	44	48
DCV/ASV/beclabuvir	0	2	2
Elbasvir/grazoprevir	0	3	3
Glecaprevir/pibrentasvir	3	45	48
SOF/VEL	0	2	2
SOF/VEL/RBV	0	1	1
Total	15	209	224

DAA, direct-acting antiviral; ASV, asunaprevir; DCV, daclatasvir; SOF, sofosbuvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; P, psychiatric disorder; NP, nonpsychiatric disorder.

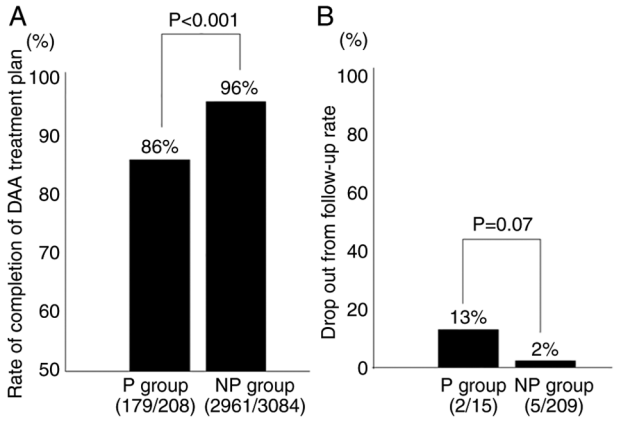

Figure 2. Comparison of the rate of completion of planned direct-acting antiviral treatment and the drop-out from follow-up. (A) Comparison of the rate of completion of direct-acting antiviral treatment planned between the P and NP groups. The result in parentheses represents the number of real treatment weeks/number of planned weeks. (B) Comparison of the drop-out from follow-up rate between P and NP groups. The result in parentheses represents the number of drop-out cases/the total number of cases. P, psychiatric disorder; NP, nonpsychiatric disorder.

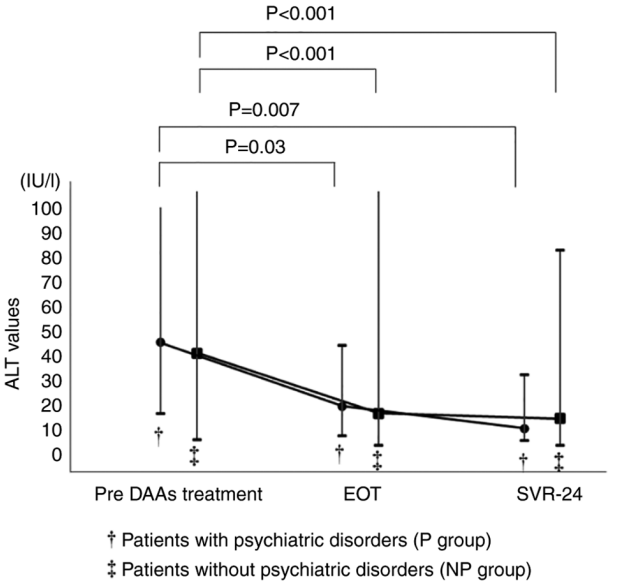

Figure 3. Time course of ALT values from patients with chronic hepatitis C virus infection during the follow-up period. Data were analyzed using Friedman's test. Closed circles show the patients with psychiatric disorders. The closed squares show the patients without psychiatric disorders. DAA, direct-acting antiviral; EOT, end of treatment with DAAs; ALT, alanine transaminase; SVR-24, undetectable hepatitis C virus RNA throughout 24 weeks of the post-treatment follow-up period.

incomplete treatment because of the development of hepatocellular carcinoma (two cases, 10 and 20 weeks of treatment, respectively), skin rash (two cases, 2 and 7 weeks of treatment, respectively), the elevation of creatine (one case, 16 weeks of treatment), development of ascites (one case, 4 weeks of treatment), continuous detectable HCV RNA level in the serum at 12 weeks after DAA treatment start (one case, 12 weeks of treatment), treatment discontinuation requested by the patient (one case, 10 weeks of treatment), the elevation of ALP (one case, 4 weeks of treatment), vomiting (one case, 1 week of treatment), the onset of malignant lymphoma (one case, 20 weeks of treatment), general fatigue (one case, 19 weeks of treatment) and the onset of herpes zoster (one case, 5 weeks of treatment). The rate of completion of the DAA treatment planned was compared between groups P and NP (Fig. 2A). Completion of DAA treatment as scheduled was less achieved in group P (86%) than in group NP (96%) (P<0.001). On the other hand, of the patients treated with DAAs, two in the group P and 5 in group NP were lost-to-follow-up; however, there was no significant difference between the two groups (Fig. 2B). There was neither discontinuation nor reduction of medications for psychiatric disorders during DAA treatment in the group P. In addition, there were no new psychiatric changes and no exacerbations of existing psychiatric disorders during DAA treatment in both groups.

Sustained virologic response at 24 weeks (SVR-24) in patients with and without a psychiatric disorder. Of all 224 cases, 200 cases (89.2%) achieved SVR at 24 weeks (SVR-24) after the end of DAA treatment (Table III). Of the 15 group P cases, 12 achieved SVR-24 and of the 209 group NP cases,

Table III. Comparison of the SVR rate between P and NP groups.

Group	Number of SVR	Number of non-SVR	SVR/total	SVR rate, %
P	12	3	12/15	80.0[a]
NP	188	21	188/209	90.0[a]
Total	200	24	200/224	89.2

[a]P=0.21, Fisher's exact test. P, psychiatric disorder; NP, nonpsychiatric disorder; SVR, sustained virological response.

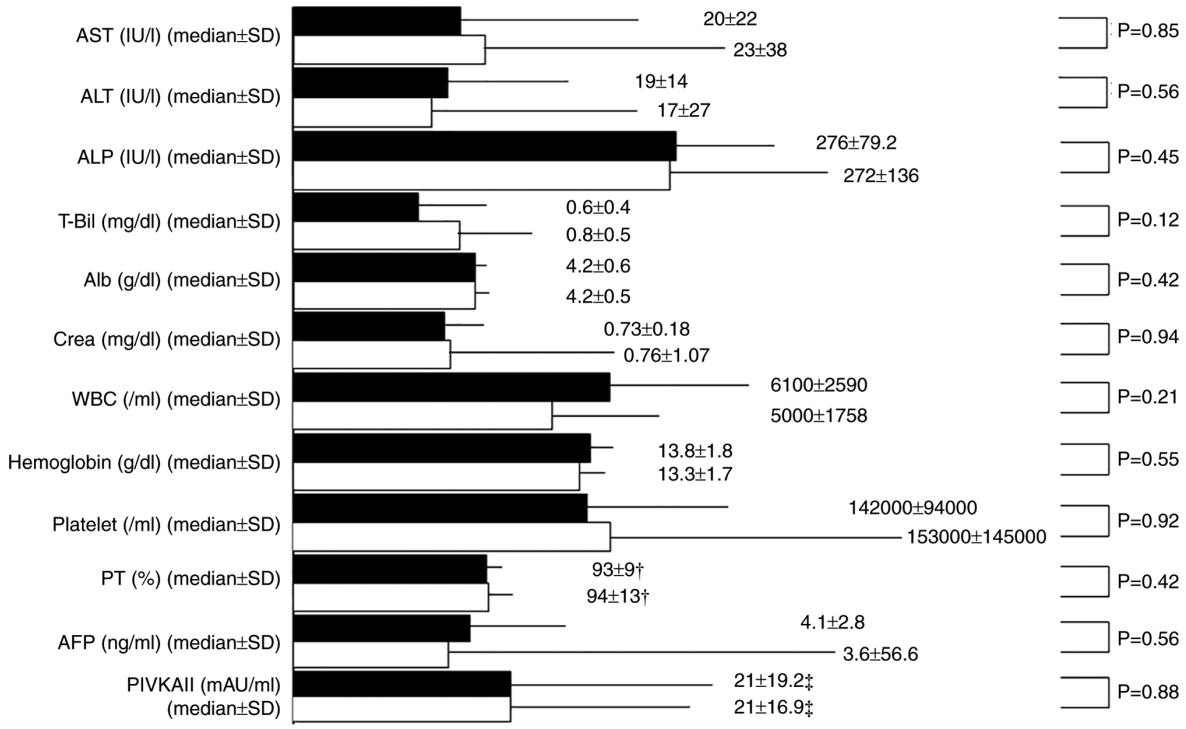

Figure 4. Comparison of the laboratory data at the end of DAA treatment (EOT) between the psychiatric disorder group (P group) and the non-psychiatric disorder group (NP group). The black columns represent the P group and the white columns represent the NP group. †Exclusion of anticoagulant (including warfarin) therapy cases. ‡Exclusion of warfarin therapy cases. P, psychiatric disorder; NP, nonpsychiatric disorder; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; T-Bil, total bilirubin; Alb, albumin; Crea, cotinine; WBC, white blood cells; PT, prothrombin time; AFP, α-fetoprotein; PIVKAII, protein-induced vitamin K absence or antagonist-II.

188 achieved SVR-24. The SVR-24 rate was 80 and 90% in groups P and NP, respectively, with no significant difference (Table III). The three group P cases who had not achieved SVR included two drop-out cases and the 21 group NP cases who had not achieved SVR included five drop-out cases. Since these drop-out patients had completed anti-viral treatment, but they did not come to the hospital after anti-viral treatment completion, it was not possible to determine whether they achieved SVR 24. In addition, the reasons for stopping their visits to the hospital could also not be ascertained. Excluding lost-to-follow-up cases, SVR-24 was achieved in 12/13 (92.3%) group P cases vs. 188/204 (92.1%) group NP cases, with no significant difference between the two groups (P>0.99).

When the chronological changes of ALT values in the SVR-24 achievement cases in both groups were compared, the ALT values were decreased after DAA treatment (Fig. 3). The chronological changes of ALT values were significant in both groups. However, the laboratory data including ALT values were not significantly different between the two groups at the end of DAA treatment (EOT) (Fig. 4). Similarly, the laboratory data at SVR-24, except for the ALT values, were not significantly different between the two groups (Fig. 5).

Discussion

Since interferon-free DAA therapy became available in 2014, SVR has been achieved in 78-100% of patients with chronic HCV infection in several studies and real-world clinical practice (7,21). In the present study, ~90% of HCV infection cases achieved SVR-24. Therefore, the HCV population including cases with psychiatric disorders in the present study tended to be similar to that reported in other studies. The SVR-24 rate was slightly less in group P than in group NP, but there was no significant difference. The SVR-24 rate of the two groups was similar, 92.3 and 92.1%, respectively, when the analysis excluded the drop-out cases. All cases lost-to-follow-up with

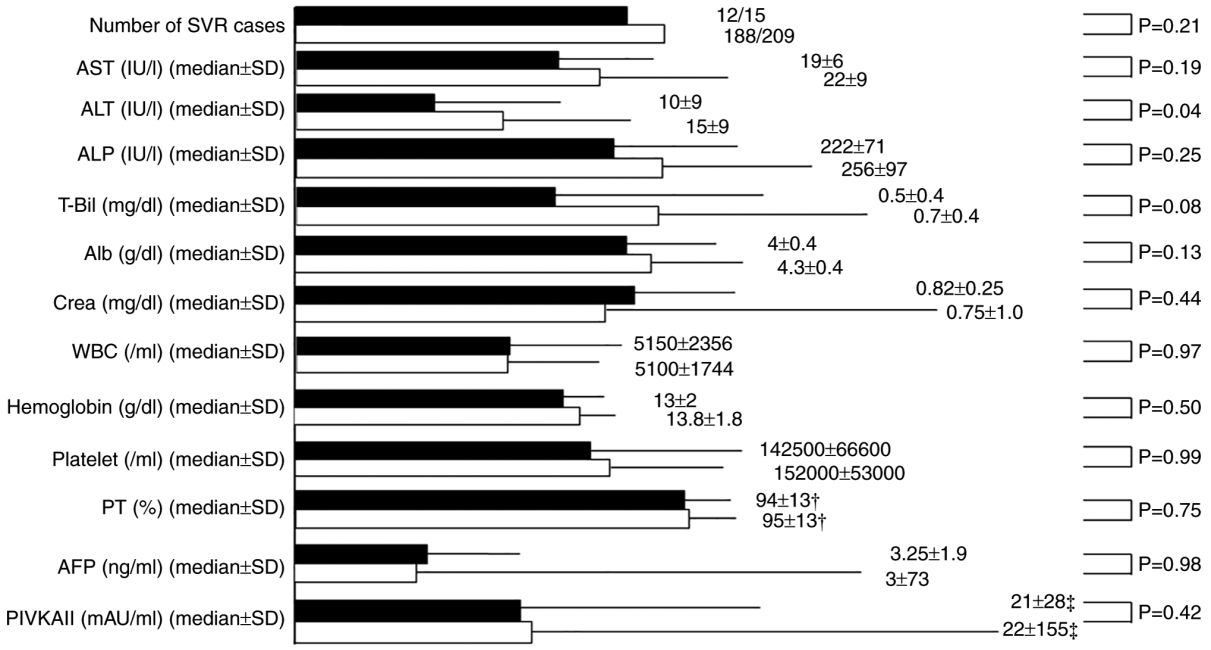

Figure 5. Comparison of the laboratory data on the sustained virological response (SVR) between the psychiatric disorder group (P group) and the non-psychiatric disorder group (NP group). The black columns represent the P group and the white columns represent the NP group. †Exclusion of anticoagulant (including warfarin) therapy cases. ‡Exclusion of warfarin therapy cases. P, psychiatric disorder; NP, nonpsychiatric disorder; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; T-Bil, total bilirubin; Alb, albumin; Crea, cotinine; WBC, white blood cells; PT, prothrombin time; AFP, α-fetoprotein; PIVKAII, protein-induced vitamin K absence or antagonist-II.

psychiatric disorders occurred after DAA treatment completion and no adverse events leading to DAA discontinuation and DAA-related serious adverse events were found in the lost-to-follow-up cases. Because hepatic enzyme values decreased after DAA treatment and DAA treatment also ameliorated hepatitis in both groups, it appears that DAA treatment for HCV infection in patients with psychiatric disorders was as effective, tolerable and safe, as it was for patients without psychiatric disorders. Sackey *et al* (18) also reported that treatment with DAAs was not associated with psychiatric decompensation in patients with hepatitis C virus infection and pre-existing mental illnesses. It was suggested that HCV positivity is a potential risk factor for the development of psychiatric disorders (13-15); therefore, DAA treatment for patients with psychiatric disorders should be started as soon as possible.

Although there was no significant difference between the two groups, there were more cases lost to follow-up in group P than in group NP. If the number of cases in group P was to increase, more lost-to-follow-up cases would occur and adversely affect the drop-out rate or the SVR-24 rate. Unfortunately, medication nonadherence is common in patients with psychiatric disorders (22-24). The patient-psychiatrist relationship could be particularly relevant for adherence in patients with a psychiatric disorder (24). In addition, Sakamaki *et al* (25) reported the appearance of psychiatric symptoms in patients with underlying psychiatric problems after DAA treatment and suggested that close monitoring is necessary for these patients (25). In the present study, no mental status changes or psychiatric problems appeared during and after DAA treatment in both cases with and without psychiatric disorders. However, hepatologists should seriously consider the patients' mental status for DAA treatment and follow-up while contacting a psychiatrist frequently. In the present study, T-Bil elevation appeared just after the start of DAA treatment in one group P case. After cessation of DAA treatment, the T-Bil level recovered to the normal range. Whether this elevation of T-Bil was attributed to the interaction of DAAs with psychiatric medications was unclear. No abnormal liver function enzyme values were detected during DAA treatment in other cases, but psychiatric patients should be carefully followed up during DAA treatment in coordination with a pharmacologist and a psychiatrist.

The present study has some limitations. The sample size was small and the study was conducted in a single center. In addition, this was a retrospective study. However, the results of this study were obtained from real-world clinical practice and this is the first report of DAA treatment for HCV infection in psychiatric patients in Asia including Japan. More cases need to be evaluated in a prospective, randomized study in the future. In addition, more detailed analyses of psychiatric changes after DAA treatment, especially after SVR, may be important in collaboration with psychiatrists. Since individuals with psychiatric diseases have high HCV seroprevalence (26) and the Asian region has a large population and higher HCV infection rate than other regions (27), it is expected that several patients with latent psychiatric diseases need treatment for HCV in Asia.

In conclusion, the results of DAA treatment for HCV infection in psychiatric patients were analyzed and its effectiveness, tolerability, and safety were similar in psychiatric patients and nonpsychiatric patients. DAA treatment can result in a high SVR rate for psychiatric patients with HCV infection. Therefore, DAA treatment should be aggressively started for psychiatric patients with HCV infection and eliminate HCV. Moreover,

progression to end-stage liver diseases, namely, hepatocellular carcinomas, liver cirrhosis, or liver failure should be prevented.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HO was involved in the conception and design of the study, and the writing and preparation of the manuscript and tables. TT, HA, ST, HK, YI, HT, SM, TSase, TSaito, KM and AN collected the data. HO and AN confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Suzuka General Hospital.

Patient consent for publication

Oral informed consent, including the statement of agreement to the use of their samples in scientific research was obtained from each patient at the first medical examination in the Outpatient Department of Suzuka General Hospital.

Competing interests

The authors declare that they have no competing interests.

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