# Genotype distribution, clinical characteristics, and racial differences observed in chronic hepatitis C patients in Pingtung, Taiwan

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## Abstract

**Background:** The World Health Organization (WHO) set out to eliminate hepatitis C virus (HCV) infection by 2030, a goal Taiwan might achieve before 2025. Using effective direct antiviral agents (DAAs) against chronic hepatitis C (CHC) in Taiwan, the treatment of CHC has been initiated in rural areas. Here, we aimed to elucidate the clinical and virological characteristics of HCV infection, and the treatment efficacy of DAAs in patients from Pingtung county in southern Taiwan.

**Methods:** A total of 152 chronic hepatitis patients treated with DAAs were consecutively enrolled. Baseline characteristics and therapeutic efficacy were evaluated.

**Results:** HCV genotype 2 was the most common viral genotype (39.5%), followed by 1b (36.8%), 6 (10.5%), and 1a (9.2%). The sustained virological response (SVR) rate was 98.7%. Hakka patients accounted for 22.4% of the study cohort, of which 14.7% had HCV genotype 6. There were no differences in clinical characteristics between Hakka and non-Hakka patients. Patients with HCV genotype 6 were younger in age (OR/CI: 0.95/0.91-1.00, $p$ = 0.04) and composed of more people who inject drugs (PWID) (OR/CI: 17.6/3.6-85.5, $p$ <0.001), when compared with other patients.

**Conclusion:** We demonstrated that DAA therapy can achieve a 98.7% SVR rate among CHC patients in Pingtung county of southern Taiwan, with a relative higher prevalence of genotype 6. The most important factor attributed to genotype 6 infection was PWID.

**Keywords:** Chronic hepatitis C; Direct antiviral agents, genotype 6; Pingtung; Sustained virological response

## 1. INTRODUCTION

The global prevalence of hepatitis C virus (HCV) infection is estimated to be in millions.[1] Patients with chronic hepatitis C (CHC) are at risk of developing dangerous complications including liver-related mortality and hepatocellular carcinoma (HCC).[2,3] Taiwan was an endemic area of HCV infection, especially among southern part of Taiwan.[4] There are different genotypes associated with HCV; the predominant HCV genotype in Taiwan was 1b, followed by genotype 2, as previously reported.[5] Different HCV genotypes may present with different outcomes.[6] Genotype 6 has a high prevalence in Southeast Asia but is rare in Taiwan,[7] and people who inject drugs (PWID) are reported to be at a higher risk for being infected with genotype 6.[8] Additionally, the natural history of cirrhosis in patients infected with genotype 6 is associated with a higher incidence of HCC.[9] In the era of direct antiviral agents (DAAs), the sustained virological response (SVR) rate is generally more than 95% in most populations.[10,11] Pangenotypic DAA treatments have been developed with extremely high therapeutic efficacy across all HCV genotypes.[12] The reimbursement for DAAs by the

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National Health Insurance (NHI) started in 2017.[13,14] Nevertheless, there remained a huge gap toward HCV elimination.[15] Pingtung is a multiracial county located in the southernmost part of Taiwan. Recently, many immigrants from Southeast Asia have settled here. Moreover, according to the official statement of the Pingtung government, the Hakka people account for about 24% of the Pingtung population.[16] The genotype of HCV in Pingtung has not previously been described. Therefore, we aimed to elucidate the clinical and virological characteristics and therapeutic efficacy of DAAs in patients from Pingtung and the Hakka population.

## 2. METHODS

### 2.1. Patients

A total of 152 CHC patients receiving DAA treatments were consecutively recruited at the outpatient clinic from a governmental hospital in Pingtung from January 2017 to November 2019. All patients received oral DAAs based on either the National Insurance reimbursement criteria of Taiwan, or regional guidelines.[17–20] Hakka patients were identified either from face-to-face interviews or based on conventional living regions. All the recruited patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Kaohsiung Medical University Hospital.

### 2.2. Laboratory and Histological Analyses

Biochemical analyses were performed using a multichannel autoanalyzer (Hitachi Inc, Tokyo, Japan). Hepatitis B surface antigen (HBsAg) was examined using a standard quantitative chemiluminescent microparticle immunoassay (ARCHITECT HBsAg, Abbott Diagnostics). Clinical relapse of HBV was defined as HBV DNA > 2000 IU/mL and ALT > 2 times upper limit of normal. HCV antibodies (anti-HCV) were measured using third-generation enzyme immunoassay (Abbott Laboratories, North Chicago, IL). HCV RNA and genotypes were measured using real-time PCR (RealTime HCV; Abbott Molecular, Des Plaines, IL).[21] SVR was defined as HCV RNA levels < the lower limit of quantification (LloQ, 12 IU/mL) at 12 weeks after the end of treatment. Anti-hepatitis D virus (HDV) immunoglobulin G (IgG), determined via the anti-HDV enzyme-linked immunosorbent assay kit (General Biologicals Corporation, Taiwan),[22] was assessed if patients tested positive for HBsAg. Liver cirrhosis was diagnosed based on either the presence of clinical, laboratory, radiological, or endoscopic findings, or the evidence of portal hypertension or cirrhosis.[23]

### 2.3. Statistical Analyses

Frequencies were compared between groups using the $\chi^2$ test with the Yates correction or the Fisher's exact test. Group means are presented as the mean ± standard deviation and were compared via analysis of variance, Student's t-test, or the nonparametric Mann-Whitney test. A fibrosis-index 4 (FIB-4) was calculated using the following formula: [age (years) × aspartate aminotransferase (AST in U/L)]/[(platelets in $10^9$/L) × {alanine transaminase (ALT in U/L)}$^{1/2}$]. A stepwise logistic regression analysis was applied to assess the factors associated with different genotypes and races. A Cochran-Armitage trend test was used to assess the trend of genotype distribution in different races. Statistical analyses were performed using the SPSS 20 statistical package (SPSS, Chicago, IL). All the statistical analyses were based on two-sided hypothesis tests with statistical significance of $p < 0.05$.

## 3. RESULTS

### 3.1. Patient Characteristics

As shown in Table 1, the mean age was 59.2 years (range: 18–83 years), with men comprising 52% (n = 79) of the cohort. The seropositive rate of HBsAg was 4.6% (N = 7), with one of the seven patients (14.3%) being anti-HDV seropositive. HCV genotype 2 (HCV-2) was the most common viral genotype (39.5 %), followed by HCV-1b (36.8%), HCV-6 (10.5%), and HCV-1a (9.2%). The rate of PWID was 5.9% (N = 9), with the majority having genotype 6 (66.7%), followed by genotype 1b (33.3%). The most commonly used DAA regimen was sofosbuvir plus ledipasvir (23.0%), followed by glecaprevir/pibrentasvir (22.4%) and elbasvir/grazoprevir (19.7%). The SVR rate for the remaining patients was 98.7% (150/152). Only two patients did not achieve SVR after treatment: one received sofosbuvir/ribavirin for 12 weeks, and the other one only received 3 weeks of glecaprevir/pibrentasvir owing to side effects (skin itch). HCV-2a patient did not achieve SVR after treatment with sofosbuvir/ribavirin for 12 weeks, per the Taiwanese guideline by NHI. The information, including the usage of various DAAs for various HCV genotype and the respective SVR rate, was described in Table S1 http://links.lww.com/JCMA/A65.

**Table 1.**

**Characteristics of the 152 chronic hepatitis C patients**

| | All patients (n = 152) |
|---|---|
| Age (y, mean (SD)) | 59.2 (12.3) |
| Male, n (%) | 79 (52) |
| AST (IU/L, mean (SD)) | 63.7 (44.7) |
| ALT (IU/L, mean (SD)) | 72.8 (69.4) |
| Platelet count (×$10^3$ μ/L, mean (SD)) | 193.2 (93.1) |
| Creatinine (mg/dL, mean (SD)) | 1.0 (1.0) |
| HBsAg seropositivity, n (%) | 7 (4.6) |
| Anti-HDV seropositivity, n (%) | 1 (0.7) |
| HCV RNA (log IU/mL, mean (SD)) | 5.6 (1.1) |
| HCVs genotype, n (%) | |
| 1a | 14 (9.2) |
| 1b | 56 (36.8) |
| 2 | 60 (39.5) |
| 3 | 5 (3.3) |
| 6 | 16 (10.5) |
| Mixed | 1 (0.7) |
| PWID, n (%) | 9 (5.9) |
| Liver cirrhosis, n (%) | 33 (21.7) |
| HCC history, n (%) | 2 (1.3) |
| FIB-4 (mean (SD)) | 3.3 (3.1) |
| FIB-4, n (%) | |
| <6.5 | 136 (89.5) |
| ≧6.5 | 16 (10.5) |
| DAA regimen, n (%) | |
| PrOD ± ribavirin | 7 (4.6) |
| Elbasvir/grazoprevir | 30 (19.7) |
| Sofosbuvir/ledipasvir ± ribavirin | 35 (23.0) |
| Sofosbuvir/ribavirin | 19 (12.5) |
| Sofosbuvir/velpatasvir ± ribavirin | 27 (17.8) |
| Glecaprevir/pibrentasvir | 34 (22.4) |
| SVR rate, n (%)† | 150 (98.7) |

†One received sofosbuvir/ribavirin, and the other one did not complete the therapy of glecaprevir/pibrentasvir owning to side effects.

SD = standard deviation; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; PWID = people who inject drugs; HCC = hepatocellular carcinoma; FIB-4 = fibrosis-4 index; DAA = direct antiviral agents; PrOD = Paritaprevir/ritonavir/ombitasvir with dasabuvir; SVR = sustained virological response.

### 3.2. Clinical Characteristics of CHC Patients Between Different Races

Hakka patients accounted for 22.4% of the patient cohort. There were no differences in the clinical characteristics between Hakka and non-Hakka patients. Additionally, there was no significant

**Table 2.**

**Characteristics of the 152 chronic hepatitis C patients between different races**

| | Hakka (n = 34) | Non-Hakka (n = 118) | *p* |
|---|---|---|---|
| Age (y, mean (SD)) | 56.7 (13.0) | 60.0 (12.0) | 0.16 |
| Male, n (%) | 22 (64.7) | 57 (48.3) | 0.12 |
| AST (IU/L, mean (SD)) | 61.4 (44.0) | 64.4 (45.1) | 0.73 |
| ALT (IU/L, mean (SD)) | 71.6 (69.4) | 73.2 (69.6) | 0.91 |
| Platelet count ($\times 10^3$ μ/L, mean (SD)) | 221.3 (141.8) | 185.1 (72.3) | 0.16 |
| Creatinine (mg/dL, mean (SD)) | 0.9 (0.3) | 1.1 (1.1) | 0.43 |
| HBsAg seropositivity, n (%) | 2 (5.9) | 5 (4.2) | 0.65 |
| Anti-HDV seropositivity, n (%) | 0 (0) | 1 (0.9) | 1.00 |
| HCV RNA (log IU/mL, mean (SD)) | 5.5 (1.1) | 5.6 (1.1) | 0.56 |
| HCVs genotype, n (%) | | | |
| 1a | 6 (17.6) | 8 (6.8) | 0.44 |
| 1b | 12 (35.3) | 44 (37.3) | |
| 2 | 10 (29.4) | 50 (42.4) | |
| 3 | 1 (2.9) | 4 (3.4) | |
| 6 | 5 (14.7) | 11 (9.3) | |
| Mixed | 0 (0) | 1 (0.8) | |
| PWID, n (%) | 1 (2.9) | 8 (6.8) | 0.69 |
| Liver cirrhosis, n (%) | 6 (17.6) | 27 (22.9) | 0.64 |
| HCC history, n (%) | 0 (0) | 2 (1.7) | 1.00 |
| FIB-4 (mean (SD)) | 2.7 (2.2) | 3.4 (3.3) | 0.25 |
| FIB-4, n (%) | | | |
| <6.5 | 30 (88.2) | 106 (89.8) | 0.76 |
| ≧6.5 | 4 (11.8) | 12 (10.2) | |
| FIB-4, n (%) | | | |
| <3.25 | 25 (73.5) | 77 (65.3) | 0.41 |
| ≧3.25 | 9 (26.5) | 41 (34.7) | |
| SVR rate, n (%) | 34 (100) | 116 (98.3) | 1.00 |

SD = standard deviation; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C virus; PWID = people who inject drugs; HCC = hepatocellular carcinoma; FIB-4 = fibrosis-4 index; SVR = sustained virological response.

difference in the distribution of HCV genotypes between Hakka and non-Hakka patients (Table 2; Fig. 1).

### 3.3. Clinical Characteristics of CHC Patients Between Genotype 6 and Other Genotypes

Compared with non-HCV-6 patients, HCV-6 patients were younger (50.3 vs 60.3 years, $p = 0.002$), had a higher proportion of PWID (37.5% vs 2.2%, $p < 0.001$), and a lower proportion of liver cirrhosis (0% vs 24.3%, $p = 0.02$) (Table 3). Multivariate analysis revealed that HCV-6 patients were younger (OR/CI: 0.95/0.91-1.00, $p = 0.04$) and had a higher proportion of PWID (OR/CI: 17.6/3.6-85.5, $p < 0.001$). There was no difference in the SVR rates among HCV-6 and non-HCV-6 patients.

### 3.4. Clinical Characteristics of Cirrhotic and Noncirrhotic CHC Patients

Compared with noncirrhotic patients, cirrhotic patients were older (63.2 vs 58.2 years, $p = 0.04$), had higher AST (80.2 vs 59.2 IU/L, $p = 0.02$), lower platelet count (112.7 vs 215.5 $\times 10^3$ μ/L, $p < 0.001$), a higher proportion of HBsAg seropositivity, and a higher prevalence of HCC (Table 4). Multivariate analysis revealed that cirrhotic patients had a higher proportion of HBsAg seropositivity (OR/CI: 8.16/1.01-66.2, $p = 0.049$) and lower platelet count (OR/CI: 0.97/0.96-0.98, $p < 0.001$).

### 3.5. Adverse Events When Receiving DAA Therapy

The most common side effects of DAA was skin itch (13.2%) and headache (9.2%) (Table 5). There were no DAA-related serious adverse event or death. Only two patients presented total bilirubin >3 mg/dL during received DAA therapy but recovered after cessation DAA for 1 week, and both of them completed the DAA therapy. There was also no HBV clinical relapse in the cohort.

## 4. DISCUSSION

In the current study, we demonstrated that HCV-6 has a relatively high incidence among CHC patients in Pingtung and could account for up to 15% of cases in Hakka patients. There was no significant difference in genotype distribution among Hakka and non-Hakka patients. The most essential factor attributed to HCV-6 infection was PWID.

The prevalence of HCV infection in Taiwan was estimated to be about 2–5%.[24,25] There are six HCV genotypes, with 1b and 2 being the most prevalent genotypes in Taiwan.[26] In this study, HCV-2 had a higher prevalence than HCV-1b. While HCV-6 is endemic in some Southeast Asian countries,[7] its prevalence in Taiwan is only about 0.5%, with some areas potentially having a higher prevalence.[1,27,28] In this study, the prevalence of HCV-6 was about 10%, which is higher than its general prevalence in Taiwan patients and showed no difference between Hakka and non-Hakka patients. HCV-6 was reported to be associated with PWID in Taiwan.[8,29] PWID accounted for 37.5% of the HCV-6 patients in our study, which is similar to other studies.[27] HCV-6 patients were younger compared with other genotypes in the cohort, and all HCV-6 patients did not have cirrhosis.

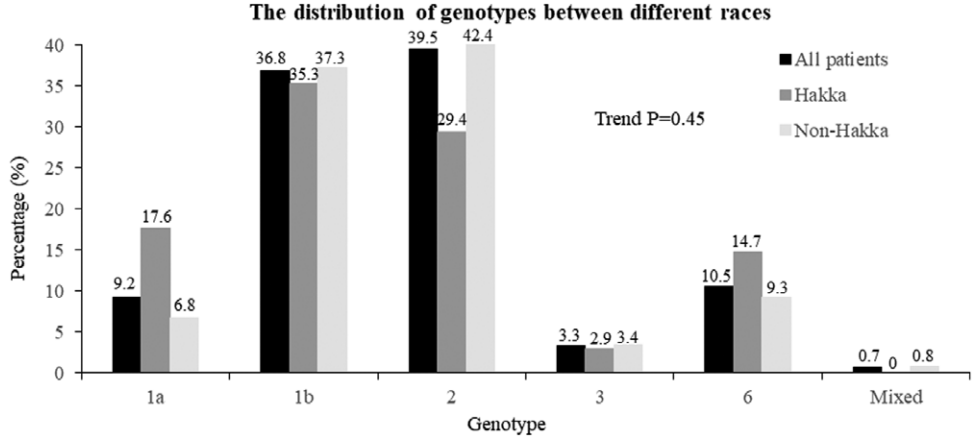


**Fig. 1** The distribution of HCV genotypes across different races.

**Table 3.**

**Characteristics of the 152 chronic hepatitis C patients between different genotypes**

| | Genotype 6 (n = 16) | Other genotypes (n = 136) | p | Logistic regression analysis | | |
|---|---|---|---|---|---|---|
| | | | | OR | 95% CI | p |
| Age (y, mean (SD)) | 50.3 (11.1) | 60.3 (12.0) | 0.002 | 0.95 | 0.91-1.00 | 0.04 |
| Male, n (%) | 10 (62.5) | 69 (50.7) | 0.44 | | | |
| AST (IU/L, mean (SD)) | 59.3 (40.7) | 65.3 (45.3) | 0.71 | | | |
| ALT (IU/L, mean (SD)) | 55.3 (32.8) | 74.9 (72.2) | 0.48 | | | |
| Platelet count ($\times 10^3$ μ/L, mean (SD)) | 226.4 (81.2) | 189.3 (93.7) | 0.10 | | | |
| Creatinine (mg/dL, mean (SD)) | 0.9 (0.3) | 1.0 (1.0) | 0.66 | | | |
| HBsAg seropositivity, n (%) | 1 (6.2) | 6 (4.4) | 0.55 | | | |
| Anti-HDV seropositivity, n (%) | 0 (0) | 1 (0.7) | 1.00 | | | |
| HCV RNA (log IU/mL, mean (SD)) | 5.5 (1.0) | 5.6 (1.1) | 0.65 | | | |
| PWID, n (%) | 6 (37.5) | 3 (2.2) | <0.001 | 17.6 | 3.6-85.5 | <0.001 |
| Liver cirrhosis, n (%) | 0 (0) | 33 (24.3) | 0.02 | | | |
| HCC history, n (%) | 0 (0) | 2 (1.5) | 1.00 | | | |
| FIB-4 (mean (SD)) | 2.2 (1.6) | 3.4 (3.2) | 0.09 | | | |
| FIB-4, n (%) | | | | | | |
| <6.5 | 16 (100) | 120 (88.2) | 0.22 | | | |
| ≧6.5 | 0 (0) | 16 (11.8) | | | | |
| FIB-4, n (%) | | | | | | |
| <3.25 | 12 (76.0) | 90 (66.2) | 0.58 | | | |
| ≧3.25 | 4 (25.0) | 46 (33.8) | | | | |
| SVR rate, n (%) | 16 (100) | 134 (98.5) | 1.00 | | | |
| Hakka people | 5 (31.2) | 29 (21.3) | 0.36 | | | |

SD = standard deviation; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C virus; PWID = people who inject drugs; HCC = hepatocellular carcinoma; FIB-4 = fibrosis-4 index; SVR = sustained virological response.

**Table 4.**

**Characteristics of the 152 chronic hepatitis C patients between cirrhotic or noncirrhotic patients**

| | Cirrhosis (n = 33) | Noncirrhosis (n = 119) | p | Logistic regression analysis | | |
|---|---|---|---|---|---|---|
| | | | | OR | 95% CI | p |
| Age (y, mean (SD)) | 63.2 (10.8) | 58.2 (12.5) | 0.04 | | | |
| Male, n (%) | 17 (51.5) | 62 (52.1) | 1.00 | | | |
| AST (IU/L, mean (SD)) | 80.2 (44.5) | 59.2 (43.9) | 0.02 | | | |
| ALT (IU/L, mean (SD)) | 72.1 (56.2) | 73.0 (72.8) | 0.95 | | | |
| Platelet count ($\times 10^3$ μ/L, mean (SD)) | 112.7 (51.3) | 215.5 (89.8) | <0.001 | 0.97 | 0.96-0.98 | <0.001 |
| Creatinine (mg/dL, mean (SD)) | 1.0 (1.0) | 1.0 (1.0) | 0.95 | | | |
| HBsAg seropositivity, n (%) | 4 (12.1) | 3 (2.5) | 0.04 | 8.16 | 1.01-66.2 | 0.049 |
| Anti-HDV seropositivity, n (%) | 1 (3.0) | 0 (0) | 0.22 | | | |
| HCV RNA (log IU/mL, mean (SD)) | 5.5 (1.3) | 5.6 (1.0) | 0.58 | | | |
| PWID, n (%) | 0 (0) | 9 (7.6) | 0.21 | | | |
| HCC history, n (%) | 2 (6.1) | 0 (0) | 0.046 | | | |
| HCV genotype 1, n (%) | 19 (57.6) | 52 (43.7) | 0.17 | | | |
| SVR rate, n (%) | 32 (97.0) | 118 (99.2) | 0.39 | | | |
| Hakka people | 6 (18.2) | 28 (23.5) | 0.64 | | | |

SD = standard deviation; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; PWID = people who inject drugs; HCC = hepatocellular carcinoma; SVR = sustained virological response.

**Table 5.**

**Safety summary**

| Variables, n (%) | All patients (n = 152) |
|---|---|
| Permanent treatment discontinuation | 1 (0.7) |
| DAA-related serious adverse event | 0 (0) |
| DAA-related death | 0 (0) |
| Adverse events in ≥ 5% of patients | |
| Skin itch | 20 (13.2) |
| Headache | 14 (9.2) |
| Total bilirubin>3mg/dL | 2(1.3) |
| HBV clinical relapse† | 0 (0) |

†Clinical relapse was defined as HBV DNA > 2000 IU/mL and ALT >2 times upper limit of normal.
DAA = direct antiviral agents; HBV = hepatitis B virus.

Once progression to liver cirrhosis occurs, the risk of developing HCC is greater in HCV-6 patients compared with other genotypes.[9] Therefore, early detection and treatment are warranted.

The population of Pingtung is about 839,000 that comprises of multiple races. With a higher prevalence of anti-HCV in southern Taiwan, the anti-HCV seropositive rate was reported to be 3–4.6% among the Pingtung population.[4,25] Moreover, it has been shown that the Hakka people are at a greater risk for hepatitis C infection,[30] but the distribution of genotype has not previously been reported. Hakka people in Taiwan immigrated from China, especially from southeast coast of China, according to one HLA study;[31] HCV genotype 6 was relative common in southern China.[32] At recent decades, Hakka people were the relatively late immigrant in Taiwan, after the Pingpu and Minnan. The Hakka was the second largest group among the four main

ethnic groups in Taiwan and accounted for 15% of the population. Sizeable concentrations of Hakka have been in Taoyuan, Hsinchu, Kaohsiung, and Pingtung. The Hakka people account for about 24% of the Pingtung population[16]; interestingly, Hakka patients also accounted for about 22% of the cohort in this study. It has been shown that the Hakka people are at a greater risk for hepatitis C infection,[30] but the distribution of genotype has not previously been reported. Genotype 6 was considered to be associated with PWID; in this study, Hakka patients who were PWID were rare. However, it should be noted that it was difficult to unearth the entire past histories of PWID.

The current DAAs are pangenotypic therapies that can treat almost all HCV genotypes with high SVR rates.[12] In this study, we observed a very high SVR rate (98.7%), which highlights the importance of encouraging patients to receive these therapies. Only one patient, who was receiving a regimen of sofosbuvir plus ribavirin, failed to respond to treatment. Sofosbuvir plus ribavirin appears to be an inferior choice of treatment for genotype 2.[33] In our study, all HCV-6 patients achieved SVR and highly efficacious pangenotypic DAA treatments.

The prevalence of HBV infection was estimated to be greater than 10% in Taiwan[25] and was higher in special populations,[34] but gradually decreased after the implementation of HBV vaccination.[35] Coinfection of HCV and HBV was about 8–15% in Taiwan[28,36] and was a risk factor for developing liver cirrhosis,[37] which is similar to the findings of the current study. HBV reactivation after DAA therapy might occur[38]; however, we did not observe any clinical HBV relapse in the present study. HDV infection was about 2–5% among chronic hepatitis B (CHB) patients in southern Taiwan.[39] There is very little literature on HDV infection among CHC patients, and the coinfection of HBV, HCV, and HDV was less than 1% in the study.

The current study had some limitations including a relatively small case number and short-term follow-up. Although participants were enrolled at a medium-sized hospital, the DAA regimens have been kept up to date and the SVR rate was as high as reported in literature. In the present study, the distribution of the HCV genotype and the real-world clinical practice were described. Our report is the first one describing this local area for the progress of the management of the HCV infection in Taiwan, which has offered patients quite good care. Also, we revealed the management of the HCV infection in the special group of Taiwanese Hakka population, which is the second-largest group among the four main ethnic groups. The long-term outcomes, such as the incidence of HCC or metabolic effects,[40–42] in different races need to be further assessed. In conclusion, we demonstrated that DAA therapies achieve a 98.7% SVR rate among CHC patients in Pingtung county in southern Taiwan, with a relative higher prevalence of genotype 6. The most important factor attributed to genotype 6 infection was PWID.

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