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Original Article

Micro-elimination of hepatitis C virus infection in the rural and remote areas of Taiwan — A multi-center collaborative care model

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KEYWORDS
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Abstract *Introduction:* Taiwan has several hepatitis C virus (HCV) hyper-endemic areas. We aimed to evaluate the effectiveness and safety of a collaborative HCV care system with an outreach decentralized strategy among the resource-constrained rural/remote areas of Taiwan.
Methods: The pilot study was conducted in four high HCV-endemic townships in the rural/remote areas of Taoyuan, Alishan, Zhuoxi and Xiulin. Registered residents who worked or lived in the four areas and were aged 30—75 years were invited to participate in this program. Multidisciplinary HCV care teams provided outreach decentralized services of anti-HCV screening, link-to-diagnosis, and link-to-treatment with direct-acting antiviral agents (DAA). The primary end-point was sustained virological response (SVR).
Results: Of 8291 registered residents who were invited as the target population, 7807 (94.2%) subjects received anti-HCV screening, with the average anti-HCV prevalence rate of 14.2% (1108/7807) (range among four areas: 11.8%—16.7%). The rate of link-to-diagnosis was 94.4% (1046/1108) of anti-HCV-positive subjects (range: 90.9%—100%) with an average HCV-viremic rate of 55.1% (576/1046) (range: 50.0%—64.3%). The link-to-treat rate was 94.4% (544/576) in HCV-viremic subjects (range from 92.7% to 97.2%). Overall, 523 (96.1%) patients achieved an SVR (range: 94.7%—97.6%). Eventually, the overall effectiveness was 80.7% (range: 74.6%—93.1%). The presence of hepatocellular carcinoma at baseline was the only factor associated with DAA failure. The DAA regimens were well-tolerated.
Conclusion: The outreach decentralized community-based care system with DAA therapy was highly effective and safe in the achievement of HCV micro-elimination in the resource-constrained rural and remote regions, which could help us to tackle the disparity.

Introduction

Chronic hepatitis C virus (HCV) infection is a leading cause of chronic liver disease and poses a considerable health burden worldwide.[1] Recently, the introduction of direct-acting antivirals (DAAs) has dramatically improved the eligibility and efficacy of HCV treatment, achieving >90% of sustained virological response (SVR) rates[2] even in difficult-to-treat patients.[3] Given the high treatment success rate of DAAs, the WHO has set an ambitious goal of 90% of HCV patients to be diagnosed and 80% of eligible HCV patients to be treated by 2030.[4] Most countries have accelerated their efforts and implemented action plans to make the WHO HCV elimination target attainable[5] while the Taiwanese government has committed to eliminate HCV nationally by 2025.[6]

The wide variation in disease patterns across different populations renders the current implementation of the nationwide elimination plan challenging. The micro-elimination approach, a strategy of tailoring suitable guidelines toward specific at-risk population, was proposed as a pragmatic way to provide efficient HCV surveillance.[7] Currently, only a handful of countries have successfully implemented initiatives to screen and treat high-risk individuals such as persons who inject drugs,[8] as well as prisoners.[9—11] There is a strong need for more countries to devote a greater share of their experiences in planning and implementing strategies for HCV elimination.

Taiwan has one of the highest prevalence rates of HCV worldwide and has fought against HCV for a long period. Commencing January 2017, DAAs were reimbursed by Taiwan's National Health Insurance (NHI), but this was only limited to HCV patients with advanced hepatic fibrosis or compensated cirrhosis. As of 2019, the NHI broadened the reimbursement of DAAs for all HCV viremic patients in Taiwan and achieved a great SVR rate of 98.3% in the general population.[12] Several micro-elimination programs have been implemented and achieved great success among hemodialysis patients[13] as well as incarcerated patients.[14] In the past few decades, a higher prevalence of HCV and liver-related mortality rate has been reported among aboriginal populations living in mountainous and rural areas in Taiwan.[15] Given the high prevalence of HCV and limited accessibility to healthcare resources in these areas, the Taiwan government set these populations as targets for HCV micro-elimination and introduced a series of programs to enhance screening, link-to-care and treatment coverage. In the current study, we aimed to evaluate the effectiveness of a collaborative HCV care strategy among the population living in aboriginal-dominant rural and remote areas in Taiwan by using information from a multi-center real-world database. Furthermore, we examined the changes in biochemical profiles during post-treatment follow-ups.

Methods

Study population

The study subjects were enrolled from a multi-center real-world database in Taiwan. In brief, this is a government-funded program initiated in 2018 for screening and treating chronic HCV-infected patients with DAAs to achieve HCV micro-elimination in aboriginal rural and remote areas. The program was conducted in four HCV high-endemic rural

townships in Taiwan, including Taoyuan District in Kaohsiung City, Alishan Township in Chiayi County, and Zhuoxi Township and Xiulin Township in Hualien County. The four townships included 55 villages, 30 in the mountainous areas and 25 in the remote plain areas. Registered residents who worked or lived in the four areas and were aged 30—75 years without prior HCV screening were invited to participate in this program. Participants who were seropositive for antibodies against HCV (anti-HCV) at the screening stage were referred to local health bureaus or hospitals for further HCV RNA confirmation. For participants seropositive for HCV RNA, 12 weeks of sofosbuvir (SOF)/ledipasvir (LDV) with and without ribavirin (RBV), elbasvir (EBR)/grazoprevir (GZR), glecaprevir (GLE)/pibrentasvir (PIB), or SOF/velpatasvir (VEL) were prescribed. The treatment regimens were prescribed based on the indications of each regimen [2,3] and physicians' discretion. The study protocol was approved by the Institutional Review Board of St. Martin De Porres Hospital (No: STM 21B-00) and the work has been carried out in accordance with The Declaration of Helsinki. The decoding data were retrieved retrospectively.

Collaborative team for HCV management

In Taiwan, HCV care has mostly been delivered in hospitals with gastroenterology or hepatology specialists. The inconvenience of transportation and unfamiliarity with the referral hospitals hinders the willingness of patients living in rural and remote areas to receive treatments. To overcome these barriers, this program implemented a collaborative approach — multidisciplinary HCV care teams with outreach liver specialists — to provide decentralized onsite service. The effectiveness of the program was measured based on the screening rate of the target population in the community, link-to-care rate of anti-HCV seropositive subjects, receiving rate of DAA therapy and successful rate of DAA treatment (Table 1).

Outcome evaluation

Decoding clinical data were retrospectively retrieved from the medical records of patients at DAAs treatment initiation, end-of-treatment (week 12), and 12 weeks after the completion of the treatment (week 24). Demographic characteristics, HCV-related comorbidity, HCV genotype, as well as laboratory data including hemoglobin, platelet count, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and estimated glomerular filtration rate (eGFR) were collected for further assessments. The fibrosis-4 index (FIB-4) was calculated based on age, AST, ALT, and platelet count level[16] as a noninvasive marker of hepatic fibrosis.

The primary end-point was sustained virology response (SVR), defined as undetectable serum HCV RNA 12 weeks after end of DAA therapy (SVR12).

Statistical methods

Descriptive statistics were presented as frequencies and percentages for categorical variables, and mean and standard deviations for continuous variables. In order to assess the changes in biochemical profile at different time points, the biochemical measurements at weeks 12 and 24 were compared with the baseline level respectively. Wilcoxon signed-rank tests were performed to examine the statistical significance of the differences in biochemical profile by taking the repeated measurements on the same patients into account, while Chi-square tests were performed to evaluate the association between SVR12 and potential covariates related to HCV. All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Effectiveness of HCV micro-elimination program

Of the four townships included in the current study, a total of 8291 residents were selected as the target population (Taoyuan, 1092; Alishan, 2600; Zhuoxi, 1982; and Xiulin, 2617). Of them, 7807 (94.2%) subjects received anti-HCV screening (ranging from 90.6% in Xiulin to 100% in Taoyuan, Table 1). The average anti-HCV prevalence rate was 14.2% (1108/7807) (lowest in Taoyuan, 11.8% and highest in Xiulin, 16.7%). Among 1108 anti-HCV positive subjects, 1046 (94.4%) were successfully linked-to-care for HCV RNA tests (range from 90.9% to 100%). The average HCV viremic rate among anti-HCV-positive subjects was 55.1% (576/1046) (lowest in Zhuoxi, 50.0% and highest in Alishan, 64.3%). Of 576 HCV viremic subjects, 544 (94.4%) received pretreatment assessment and DAA therapy (range from 92.7% in Zhuoxi to 97.2% in Taoyuan). Overall, 523 (96.1%) DAA-treated patients achieved an SVR (range from 94.7% in Zhuoxi to 97.6% in Xiulin). Eventually, the community effectiveness was 93.1%, 86.6%, 75.7% and 74.6% in Taoyuan, Alishan, Zhuoxi, and Xiulin respectively, with an overall effectiveness of 80.7% (Table 1). The baseline characteristics were compared between anti-HCV positive patients with and without HCV viremia (Supplement Table 1).

Baseline characteristics of DAA-treated population

The baseline characteristics of the DAA-treated population are displayed in Table 2. In total, 544 HCV-viremic patients received the DAAs treatment. Among them, the mean age was 63.1 ± 12.9 years, and 62.3% of them were females. The most prevalent comorbidities were hypertension ($n = 219$, 40.3%), diabetes mellitus ($n = 155$, 28.5%), and hyperlipemia ($n = 100$, 18.4%). Twenty-nine (5.3%) patients were coinfected with hepatitis B virus (HBV) while 9 (1.7%) had human immunodeficiency virus (HIV) coinfection. One hundred and seventy-six (32.4%) had advanced hepatic fibrosis (FIB-4 > 3.25). HCC was identified in 17 (3.1%) patients before DAAs treatment. The most prevalent HCV genotype was HCV genotype 1 (49.8%), followed by HCV genotype 2 (35.5%). The mean HCV viral load was 6.1 logs IU/ml at baseline.

SVR rate and factors associated with DAA responses

Of the 544 DAA-treated patients, 523 (96.1%) patients achieved an SVR (Table 2). The baseline characteristics in terms of age, sex, BMI, the proportion of hypertension,

Table 1 HCV care cascade of HCV micro-elimination program in the aboriginal rural and remote areas of Taiwan.

Township	Target population n	(A) Subjects receiving screening, n (%)	Anti-HCV seropositive n (%)	(B) Link-to-care n (%)	HCV RNA seropositive n (%)	(C) DAA treatment n (%)	(D) SVR12 n (%)	(E) Effectiveness
Taoyuan District	1092	1092 (100%)	129 (11.8%)	129 (100%)	72 (55.8%)	70 (97.2%)	67 (95.7%)	93.1%
Alishan Township	2600	2511 (96.6%)	319 (12.7%)	311 (97.5%)	200 (64.3%)	192 (96.0%)	184 (95.8%)	86.6%
Zhuoxi Township	1982	1833 (92.5%)	264 (14.4%)	246 (93.2%)	123 (50.0%)	114 (92.7%)	108 (94.7%)	75.7%
Xiulin Township	2617	2371 (90.6%)	396 (16.7%)	360 (90.9%)	181 (50.3%)	168 (92.8%)	164 (97.6%)	74.6%
Total	8291	7807 (94.2%)	1108 (14.2%)	1046 (94.4%)	576 (55.1%)	544 (94.4%)	523 (96.1%)	80.7%

(E) = (A) x (B) x (C) x (D).

diabetes, hyperlipidemia, HIV coinfection and HBV coinfection, HCV genotype distribution, HCV viral loads, AST and ALT levels, renal function, presence of advanced fibrosis and hepatic decompensation were all comparable between SVR and non-SVR patients (Table 2). The presence of HCC at enrollment was the only factor significantly associated with treatment failure (3/17 [17.6%] vs. 18/527 [3.4%], $P < 0.01$).

Table 2 Baseline characteristics in HCV-infected patients with and without achieving SVR after receiving direct-acting antiviral agent therapy.

Mean ± SD or N (%)	Total (n = 544)	Non-SVR (n = 21)	SVR (n = 523)	P-value
Age	63.1 ± 12.9	65.0 ± 11.2	63.0 ± 12.9	0.49
Female	339 (62.3)	12 (57.1)	327 (62.5)	0.62
BMI	27.0 ± 4.7	26.0 ± 3.5	27.0 ± 4.8	0.39
Hypertension	219 (40.3)	8 (38.1)	211 (40.3)	0.98
Diabetes	155 (28.5)	7 (33.3)	148 (28.3)	0.51
Hyperlipidemia	100 (18.4)	5 (23.8)	95 (18.2)	0.44
HIV coinfection	9 (1.7)	0 (0.0)	9 (1.7)	0.54
HBV coinfection	53 (9.7)	1 (4.8)	52 (9.9)	0.46
HCV genotype, 1/2/mixed/3/6/unclassified	270 (49.6)/193 (35.5)/31 (5.7)/6 (1.1)/42 (7.7)/2 (0.4)	10 (47.6)/7 (33.3)/2 (9.5)/0 (0.0)/2 (9.5)/0 (0.0)	260 (49.7)/186 (35.5)/29 (5.5)/6 (1.2)/40 (7.7)/2 (0.4)	0.96
HCV RNA, log_{10} IU/ml	6.1 ± 0.9	6.0 ± 0.9	6.1 ± 0.9	0.62
WBC, $x10^3u/L$	5.2 ± 4.1	5.5 ± 2.9	5.2 ± 4.1	0.74
Hb, g/dL	13.2 ± 2.1	12.3 ± 2.7	13.2 ± 2.1	0.05
PLT, $x10^3u/L$	193.7 ± 75.7	205.1 ± 112.2	193.3 ± 74.1	0.50
ALB, g/dl	4.0 ± 0.5	3.9 ± 0.5	4.0 ± 0.5	0.50
BIL(T), mg/dL	0.8 ± 0.5	1.0 ± 1.1	0.8 ± 0.5	0.43
AST, IU/L	61.6 ± 53.1	78.4 ± 62.2	60.9 ± 52.7	0.15
ALT, IU/L	64.1 ± 66.2	76.1 ± 84.8	63.6 ± 65.4	0.41
Cr, mg/dl	3.3 ± 9.2	2.0 ± 3.4	3.4 ± 9.4	0.51
eGFR, mL/min/1.73 m^2	73.1 ± 39.5	82.3 ± 41.3	72.7 ± 39.5	0.29
FIB-4	3.3 ± 3.2	3.7 ± 2.7	3.3 ± 3.2	0.59
FIB-4 > 3.25	176 (32.4)	8 (38.1)	168 (32.1)	0.46
Hepatic decompensation	3 (0.6)	0 (0.0)	3 (0.6)	0.81
Hepatocellular carcinoma	17 (3.1)	3 (14.3)	14 (2.7)	<0.01
DAA + RBV combination	80 (14.7)	6 (28.6)	74 (14.2)	0.07

Sustained virological response, SVR; Hepatitis C virus: HCV. Body Mass Index: BMI. White blood cells: WBC. Hemoglobin: Hb. Platelet: PLT. albumin: ALB. Total bilirubin: BIL(T). ALT: alanine aminotransferase. AST: Aspartate aminotransferase. Creatinine: Cr. a-Fetoprotein: AFP. eGFR: estimate GFR. Fibrosis-4: FIB-4.

Biochemical profile changes during follow-ups

Fig. 1 depicts the biochemical profile changes of different markers amongst HCV- infected patients after DAAs treatment. Compared with baseline measurements, serum AST and ALT levels significantly attenuated at the end of treatment (week 12) and maintained low levels 12 weeks after the completion of treatment (week 24). The mean difference from baseline to week 12 was −26.51 IU/L for AST ($p < 0.001$) and −33.78 IU/L for ALT ($p < 0.001$) respectively (Fig. 1A and B). Although there was no significant change of total bilirubin and direct bilirubin from baseline to week 12, significant reduction of total bilirubin and direct bilirubin levels were found from baseline to week 24, -0.08 mg/dL for total bilirubin ($p < 0.001$) and −0.05 mg/dL for direct bilirubin ($p < 0.001$) respectively (Fig. 1C and D). Significant decline of hemoglobin concentrations and eGFR levels were found at the end of treatment, −0.31 g/dL for hemoglobin ($p = 0.001$) and −4.31 for eGFR ($p < 0.001$) respectively (Fig. 1E and F); however, hemoglobin and eGFR returned to baseline levels 12 weeks after the end of treatment while platelet count increased significantly from 194×10^9/L at baseline to 201×10^9/L at week 24 ($p = 0.002$) (Fig. 1G).

Safety of treatment of direct-acting antiviral agents

Eight patients (1.3%) discontinued treatment, although no case was related to DAA therapy, with the most frequent adverse events being fatigue/malaise, headache, diarrhea, dizziness, and pruritus (Table 3).

Discussion

The current study shows the advantages of outreach screening and community HCV care system with the highly efficacious DAAs for residents living in four aboriginal-dominant rural and remote areas in Taiwan. Notably, 94.2% of the target population received anti-HCV screening, 94.4% of anti-HCV-positive subjects were successfully linked-to-care, 94.4% of HCV viremic subjects received DAA therapy, and 96.1% of DAA-treated patients achieved SVR12, with an overall community effectiveness of 80.7%. With the high screening and link-to-care rate of 94.2% and 94.4%, respectively, the treatment rate (94.4%) was much higher than the WHO goal (80%). Taken together, we demonstrate that the strategy of multidisciplinary HCV care teams with outreach decentralized onsite service could achieve the goal of WHO, with greater than 72% of HCV patients being identified and treated in all four target populations. The treatment efficacy and safety profiles were comparable to the previous report from large-scale real-world data in Taiwan.[12]

With the advent of safe and favorably tolerated DAA therapy against HCV infection, the eradication of HCV might be highly expected in the near future although most HCV treatments and surveillance are only available in hospital-based settings. A previous survey in Europe showed that only 20% of HCV-infected patients could have access to DAA therapy in non-hospital settings.[17] Healthcare inequities and disparities between urban and rural patients have been recognized as the main barriers to accessing HCV care.[18] Compared with patients in urban areas and high-income countries, HCV management is less likely to be accessible for those in rural areas and less-developed countries.[18] In Taiwan, limited public transportation networks and unfamiliarity with hospitals, particularly for the elderly living in rural or remote areas, have been reported as the key challenges in transferring rural residents with HCV infection for further examination and treatment.[19] In our patients, 32% of the HCV RNA positive cases were with advanced fibrosis (FIB-4 >3.25). These patients are at risk of end stage liver diseases, such as HCC, especially those with diabetes, aging, male and obesity.[20,21] Therefore, these patients should be monitored regularly according to the guideline.[2]

In order to overcome the huge gap between high HCV prevalence and scarce medical resources in rural and mountainous areas, we adopted an outreach decentralized HCV care for people living in these areas by establishing a community-based collaborative care team. We incorporated well-trained public health nurses and case managers to communicate with patients and convince them to accept referral for further laboratory examination and DAA treatments. Outreach gastroenterologists/hepatologists also regularly provided local HCV care for patients. Thus, our program has shown a great treatment adherence for DAAs, with over 94% of HCV-infected patients being successfully treated. This outreach treatment strategy could serve as a great exemplar for HCV micro-elimination in rural and remote areas. However, 5.5% of anti-HCV positive subjects did not receive HCV RNA testing. the implementation of an HCV RNA reflexing test is highly recommended in the special population to ensure the link-to-diagnosis rate, as reported in hospital-based HCV control.[22] We emphasized that this study has achieved the overall goal of WHO, but there are still a few people who have not completed the diagnosis and treatment. Advocating the importance of HCV eradication to our patients and implementing of an HCV RNA reflexing test is the mainstay to reduce the barriers to screening.

In recent years, a project called ECHO (Extension for Community Healthcare Outcomes) was launched by the New Mexico Health Sciences Center, which aimed to reduce health disparities and expand access to medical care for underserved populations with complex diseases.[23,24] This project demonstrated improved access to DAAs and reduced barriers to HCV treatment in areas that lacked specialist physicians. For every 100 clinician inputs for training, the initiation rate of DAA treatment was raised by 9%,[25] suggesting unmet needs for specialty services in rural and underserved areas. In our program, we were also dedicated to connecting with village leaders to collect the correct information for home visits, deliver accurate concepts about HCV screening and treatment to villagers, and ensure treatment adherence. It is suggested that leveraging local expertise could effectively improve rural HCV management.

So far, HCV micro-elimination projects conducted in rural areas are still limited. A similar project was carried out in Egypt that demonstrated the high effectiveness of using an outreach model for prevention, diagnosis, and treatment across villages in a large-scale rural

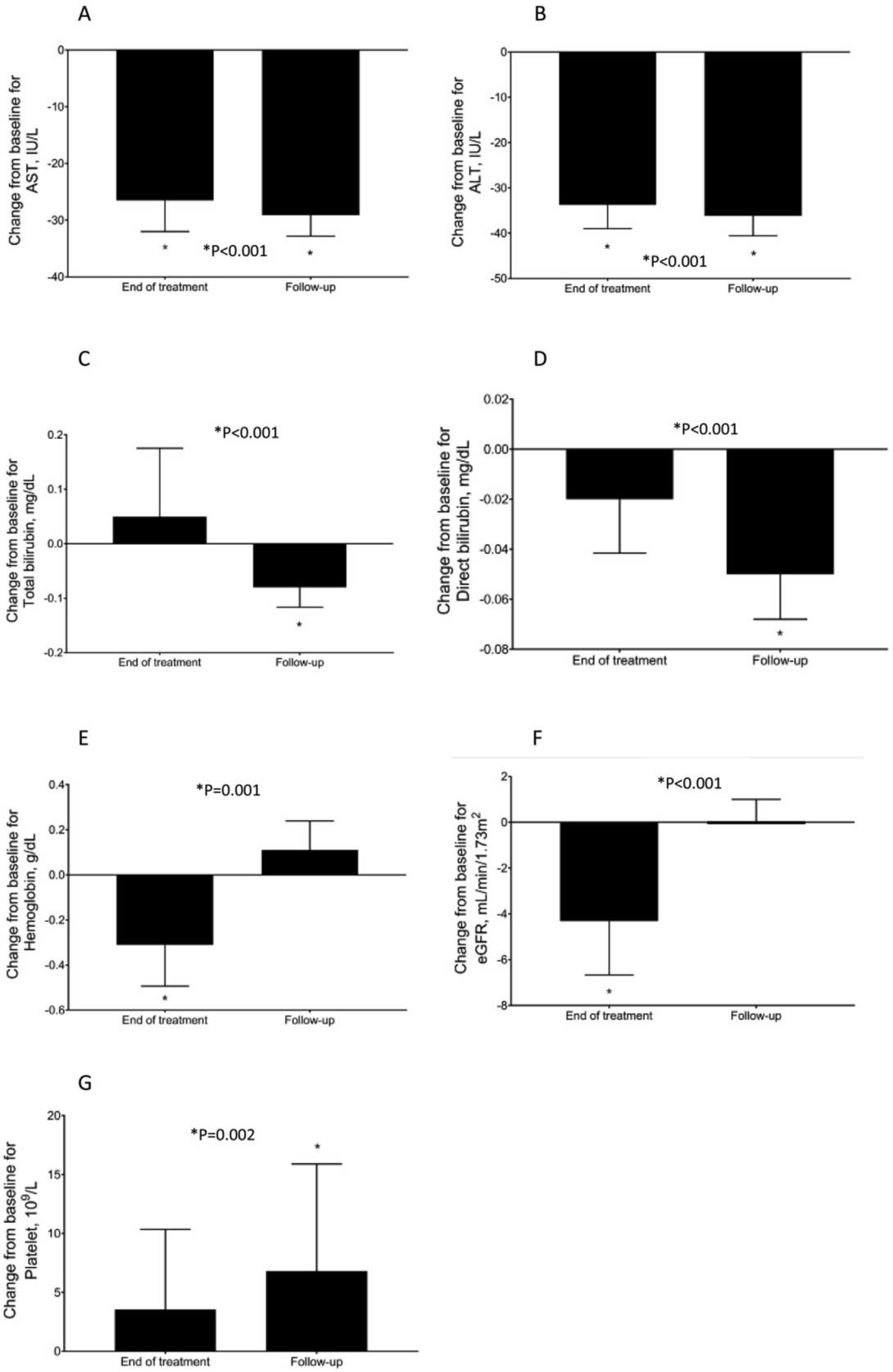

Figure 1. Mean change from baseline for biochemical measures at the end of treatment and 12 weeks after end of treatment. (A) AST, (B) ALT, (C) Total bilirubin, (D) Direct bilirubin, (E) Hemoglobin, (F) eGFR, and (G) Platelet.

Table 3 Safety profiles.

	N (%)
Treatment discontinuation	32 (1.3%)
DAA-related	0
Adverse events	
Fatigue/Malaise	41 (7.5%)
Headache	20 (3.7%)
Diarrhea	19 (3.5%)
Dizziness	17 (3.1%)
Fever	9 (1.7%)
Pruritus/skin rash/itching	9 (1.7%)
Insomnia	2 (0.4%)
Rigor	2 (0.4%)
Epigastric pain	2 (0.4%)
Myalgia	1 (0.2%)
Weakness	1 (0.2%)

community.[26,27] They employed educational and preventative approaches in 73 villages, by providing free testing as well as linkage to care and treatment while comprehensively screening 200,000 individuals and identifying an overall HCV prevalence of 7.8%. Among those who tested positive for anti-HCV, 91.2% were HCV RNA positive and immediately received treatment, with a treatment completion rate of 99.9% and SVR rate of 97%.[27]

A mere few patients failed to achieve SVR12 in the current study, and the only significant factor associated with treatment failure was the presence of HCC at the time of DAA treatment. This finding was consistent with prior large-scale real-world studies in Taiwan[12,28] as well as globally.[29] In the current study, we observed significant improvement in liver function after DAA therapy. However, eradicating HCV does not ensure the cure of the disease. A subset of patients remained at risk of cirrhosis,[30] liver-related complications[30] and HCC[31] after achieving SVR, partly due to irreversible HCV-related epigenetic signature.[32] Therefore, long-term post-SVR regular follow-up of major liver complications is mandatory, especially for high-risk patients, such as those with advanced fibrosis.[33] With the strategy of simplified, genotyping/subtyping-free, pan-genotypic anti-HCV treatment algorithms recommended by EASL[34,35] and AASLD,[36] and the retreatment regimen[3] of SOF/VEL/voxilaprevir (VOX) reimbursed by Taiwan's NHI since September 1, 2021, the care cascade of HCV infection, especially in the rural areas, will become more simple, efficient and effective in the future.

Although the current study demonstrated successful cooperation between central and local governments in HCV elimination, we encountered a limitation from only focusing on the target population of registered residents who lived in the four areas, not on registered residents who stayed or worked outside the rural/remote areas most of the time. Further strategies are warranted for HCV micro-elimination for registered residents who are not constantly living in their rural/remote areas.

In conclusion, our study revealed great effectiveness of the outreach decentralized community-based care system for HCV micro-elimination in the aboriginal-dominant rural and remote regions in Taiwan. Our findings provide insights for other countries to develop tailored policies and strategies for the goals of HCV micro-elimination in resource-constrained areas to tackle the disparity.

Declaration of competing interest

None for all authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.01.014.