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Original Article

# A people-centered decentralized outreach model toward HCV micro-elimination in hyperendemic areas: COMPACT study in SARS Co–V2 pandemic

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**Abstract** *Objectives:* Gaps in linkage-to-care remain the barriers toward hepatitis C virus (HCV) elimination in the directly-acting-antivirals (DAA) era, especially during SARS Co–V2 pandemics. We established an outreach project to target HCV micro-elimination in HCV-hyperendemic villages.

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Microelimination;
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SARS Co—V2;
Pandemic

*Methods:* The COMPACT provided "door-by-door" screening by an "outreach HCV-checkpoint team" and an "outreach HCV-care team" for HCV diagnosis, assessment and DAA therapy in Chidong/Chikan villages between 2019 and 2021. Participants from neighboring villages served as Control group.
*Results:* A total of 5731 adult residents participated in the project. Anti-HCV prevalence rate was 24.0% (886/3684) in Target Group and 9.5% (194/2047) in Control group ($P < 0.001$). The HCV-viremic rates among anti-HCV-positive subjects were 42.7% and 41.2%, respectively, in Target and Control groups. After COMPACT engagement, 80.4% (304/378) HCV-viremic subjects in the Target group were successfully linked-to-care, and Control group (70% (56/80), $P = 0.039$). The rates of link-to-treatment and SVR12 were comparable between Target (100% and 97.4%, respectively) and Control (100% and 96.4%) groups. The community effectiveness was 76.4% in the COMPACT campaign, significantly higher in Target group than in Control group (78.3% versus 67.5%, $P = 0.039$). The community effectiveness decreased significantly during SARS Co—V2 pandemic in Control group (from 81% to 31.8%, $P < 0.001$), but not in Target group (80.3% vs. 71.6%, $P = 0.104$).
*Conclusions:* The outreach door-by-door screen strategy with decentralized onsite treatment programs greatly improved HCV care cascade in HCV-hyperendemic areas, a model for HCV elimination in high-risk marginalized communities in SARS Co—V2 pandemic.


## Introduction

Hepatitis C virus (HCV) infection is one of the leading causes of liver-related clinical outcomes including liver cirrhosis, hepatocellular carcinoma (HCC) and mortality globally.[1] Successful HCV clearance by antivirals greatly reduces the risk of HCC and mortality.[2—4] The tremendous burden on public health is underestimated mainly because of low disease awareness, poor link-to-care and the lack of effective preventive measurements. Taiwan is not an exception with an estimated nationwide prevalence of 4%—9%, and the prevalence exceeds 20% in some hyperendemic areas.[5—7] Although several measurements have been vigorously implemented over the past decades, several hurdles existed in the era of interferon-based therapies on the path to successful HCV treatment, from disease awareness, diagnosis, accessibility, treatment eligibility, to treatment efficacy, leading to huge gaps in each HCV care cascade.[8]

Fortunately, the high treatment efficacy, eligibility, safety, tolerability, and easy dosing of antiviral treatments for CHC are readily accessible for HCV care owing to the launch of directly acting antivirals (DAAs).[9,10] The National Health Insurance of Taiwan started to reimburse DAAs in 2017, and the government additionally set a commitment to achieve the goal of HCV elimination by 2025, five years ahead of the World Health Organization's goal.[11] Many efforts have been made in public prevention and therapeutic intervention for HCV to achieve this goal. Most previous efforts to eliminate HCV have focused on eliminating HCV infection in terms of comprehensive HCV screening and diagnosis, and successful linkage-to-care and linkage-to-treatment with affordable DAA regimens. The efforts are of importance and of pressing need for the hyperendemic areas.[12] In addition, a recent mathematical model study showed that outreach screening and immediate onsite DAA therapy are the main effective measurements for achieving the overall goal of the WHO Global Health Sector Strategy on Hepatitis (2016—2021) by 2030.[13] We demonstrated that an outreach program of mass screening with onsite treatment for uremic patients under maintenance hemodialysis helped achieve HCV micro-elimination in hemodialysis units.[14] Nevertheless, the strategy including comprehensive diagnosis and linking patients to care has rarely been taken in the HCV hyperendemic regions.

Tzukuan is an HCV hyperendemic township located in the rural area of Kaohsiung City in southern Taiwan.[15,16] It had an extremely high anti-HCV + prevalence (>40%) among adult residents with an annual incidence rate of 4.5%.[15,16] We have reported that the age-, and sex-adjusted anti-HCV prevalence rate has been as high as 18.8%.[17] Although the adjusted anti-HCV prevalence rates reduced over time, it remains a major health threat in Tzukaun township.[17] Therefore, we established a prospective pilot project aiming to tackle the barriers in each HCV care cascade in Chidong and Chikan Villages, which possessed the highest anti-HCV prevalence rates (20.9% and 21.4%, respectively) while low disease awareness (26.2% and 14.6%, respectively) in Tzukuan.[18] The people-centered project mainly included the strategies of outreach "door-by-door" screening followed by an outreach decentralized HCV care service. We anticipated that the implementation of outreach program (COMPACT) will be a feasible model for HCV micro-elimination in the HCV hyper-endemic areas. The aim of the COMPACT study was to address the scaling up of HCV care cascade from screening, accurate diagnosis, link-to care to treatment allocation by adopting the

aforementioned strategies. Since SARS Co—V2 break out unexpectedly in March 2020, we also assessed the efficacy of the COMPACT model before and after the SARS Co—V2 pandemic.

## Methods

### Background

The target HCV hyperendemic areas were Chidong and Chikan Villages of Tzukuan, an HCV hyperendemic Township in the suburban area of Kaohsiung City in southern Taiwan.[18] The COMPACT program is a prospective, interventional study which provided mass screening and link-to-care for HCV by an outreach check-up team and onsite DAA therapy by an outreach HCV treater team January 2019 to December 2021. With the collaboration of a non-profit organization, Taiwan Liver Research Foundation, and a tertiary referral center, Kaohsiung Medical University Hospital, the program was engaged with stakeholders, local opinion leaders and providers of both healthcare and administration in Chidong/Chikan Villages and Tzukuan Township. This study aims to compare the HCV treatment uptake and community effectiveness between Target Group and the Control Group.

### Study population

All subjects aged ≥20 years and who had the willingness to participate in the program were recruited. People who live in or work in Chidong/Chikan villages were enrolled as the "Target group", while participants who live in or work in the other villages without active intervention were served as the "Control group" (Supplementary Fig. 1). The residents from the other villages of Tzukuan District will be collected according to their willingness to join the screening. The study was conducted following the Declaration of Helsinki. The ethics committee of the Kaohsiung Medical University Hospital approved the study. All participants gave written informed consent before enrollment.

### Strategies with door-by-door interventions taken in the target group

a. Task-force action plan for the announcement of COMPACT program to increase the disease awareness

Door-by-door screening information was delivered by Flier in collaboration local key opinion and administrative leaders in Chikan/Chidong Villages. The details and structured strategies of the project was released and posted on media and press. The educational programs for local healthcare providers and general population of the Township were provided to increase the rates of disease awareness and link-to-treater.

b. HCV testing/diagnosis by COMPACT outreach screening program

We first set up an outreach HCV check-up team including one physician consultant, two nursing coordinators and two administrative stuffs. There are two rounds of the screening program.

· ***The first-round screening***

The first-round comprehensive screening program consisted of two strategies. Firstly, one shop strategy: A screening team fixed in a community HCV service station at the local activity center located in the central area of Target Villages to provide a feasible screening service, six days a week, for the participants. The screening information was delivered by mail, flier, media and phone call, followed by intensified second calls for previous non-responders in the first round. Secondly, a door-by-door strategy: a mobile screening team provided a home-based screening service for the residents in Target Villages. The schedule was in collaboration with Heads of Neighborhoods. The screening was performed every two neighborhoods weekly in the first half-year.

The first-round screening program included interviews of questionnaires, blood sampling for testing viral hepatitis and liver function and linking the HCV-viremic patients to care. The blood testing included complete cell count, hepatitis B surface antigen (HBsAg), anti-HCV, transaminases, and alpha-fetoprotein for all participants. HCV RNA was tested for anti-HCV-seropositive subjects, and HCV genotyping was tested for HCV RNA-positive subjects with the strategy of HCV reflex testing.[19] Subjects who were positive for anti-HCV or HBsAg, or had abnormal liver function were appointed for transient elastography (Fibroscan, Echosens, Paris, France) performed by qualified and experienced operators following standard procedure. HCV-viremic subjects received linkage-to-care and linkage-to-treat for anti-HCV therapy scheduled by well-trained nursing specialists during the SARS Co—V2 pandemic. The residents from the other villages of Tzukuan District will be collected according to their willingness to join the screening as the Control group. They were either appointed to the COMPACT outreach HCV-treater team or referred to the other HCV treaters based on patient discretion.

· ***The second-round screening***

Subjects seropositive for anti-HCV in the first-round screening were recalled one year later for second round screening, including questionnaire interview, liver function tests, HCV RNA, AFP and the outcome of link-to-care.

c. Link-to-treater, either COMPACT outreach HCV-treater team or the other local treaters

We set up an outreach HCV-eliminating treatment team including hepatologists, nursing coordinators, pharmacists, laboratory technicians and administrative coordinators. The COMPACT outreach HCV-treater team operated in a community health-care station located in the community center of Target area. This team provided "point-of-care" service of pretreatment assessment, anti-HCV treatment and post-treatment follow-up, including liver function and renal function tests, onsite abdominal sonography, evaluation of potential drug—drug interaction. The treatment regimens and strategies conformed to the regulations of the Health and Welfare Department of Taiwan and regional guidelines.[10,14]

### Strategies and interventions taken in the control group

The strategies and intervention taken in the Control group were the same as those in the Target group, except that there was no "door-by-door" strategies for deliver the information and screening for the Control group. The information for the Control group only came from flier and media publicity.

### Endpoint measurements

The primary end-point was the proportion of successful link-to-care among all HCV-viremia subjects identified. The secondary endpoints were:1. The proportion of successful link-to-treat among all successful link-to-care subjects identified; 2. The efficacy of DAA therapy, the sustained virological response (SVR), defined as undetectable HCV RNA throughout 12 weeks post treatment.

### Laboratory analysis

Biochemical analyses were evaluated on a multichannel autoanalyzer (Hitachi Inc, Tokyo, Japan). HBsAg was tested using commercially available enzyme-linked immunosorbent assay kits (Abbott Laboratories, North Chicago, IL, USA). Anti-HCV tests were performed using a third-generation commercially ELISA kit (AxSYM 3.0; Abbott Laboratories, North Chicago, IL, USA). HCV RNA and genotype were detected using real-time PCR (Real-time HCV; Abbott Molecular, Des Plaines IL, USA; detection limit: 12 IU/ml).

### Disease severity assessment

Fibrosis-4 index (FIB-4) was calculated by (age $\times$ AST)/(platelets ($10^9$/L) $\times$ $ALT^{1/2}$).[20] Liver cirrhosis was defined as any of the following: transient elastography (FibroScan®; Echosens, Paris, France) $>$ 12 kPa, fibrosis-4 index (FIB-4) $>$ 6.5, or the presence of clinical, radiological, endoscopic, or laboratory evidence of cirrhosis and portal hypertension.[21–23]

### Statistical analysis

Frequency was compared between groups using the $\chi^2$ test with the Yates correction or Fisher's exact test. Group means (presented as the mean standard deviation) were compared using analysis of variance and Student's t-test or the nonparametric Mann–Whitney U test when appropriate. Descriptive and comparative statistics were performed for all demographic and clinical variables. The need-to-treat population was defined as the number of HCV viremic subjects plus the number of anti-HCV-seropositive and HCV RNA-negative subjects with prior history of antiviral therapy. The efficacy of DAA therapy was evaluated in an intent-to-treat (ITT) population (all subjects who received $\geq$1 dose of DAA), and a modified ITT (mITT) population (subjects receiving $\geq$1 dose of DAA with HCV RNA data available at posttreatment week 12). The community effectiveness in COMPACT was defined as proportion of HCV cure among HCV-viremic subjects. The overall treatment update was defined as proportion of HCV cure among need-to-treat subjects (anti-HCV seropositive subjects excluding those with spontaneous HCV clearance at enrollment). The statistical analyses were performed using the SPSS 12.0 statistical package (SPSS, Chicago, IL, USA). All statistical analyses were based on two-sided hypothesis tests with a significance level of $p < 0.05$.

## Results

### Baseline characteristics

By December 2020, a total of 3684 subjects were enrolled in the Target Group, and 2047 subjects were recruited in the Control group (Table 1). The mean age in the target group was 53.1 of years and male accounted for 57.4% of the population. Compared to the control group, patients in the Target group were older (53.1 years vs. 50.6 years, $P < 0.001$), had higher body mass index (25.2 kg/$m^2$ vs. 24.4 kg/$m^2$, $P < 0.001$) and FIB-4 (1.3 vs. 1.1, $P < 0.001$), higher levels of fasting sugar (92.9 mg/dL vs. 89.9 mg/dL, $P = 0.02$), hemoglobin A1C (5.9% vs. 5.8%, $P < 0.001$), hemoglobin (13.9 g/dL vs. 13.6 g/dL, $P < 0.001$), liver biochemistries including *r*-glutamyltransferase (rGT, 23.0 IU/L vs. 22.0 IU/L, $P < 0.001$), aspartate aminotransferase (AST, 27.7 IU/L vs. 25.1 IU/L, $P < 0.001$) and alanine aminotransferase (ALT, 29.6 IU/L vs. 26.1 IU/L, $P < 0.001$), lower platelet counts ($256.2 \times 10^3$ u/L vs. $262.8 \times 10^3$ u/L, $P = 0.001$) and a higher proportion of hypertension (26.7% vs. 20.7%, $P < 0.001$). The seropositivity rates of HBsAg (10.3% vs. 8.4%, $P = 0.019$) and anti-HCV (24.0% vs. 9.5%, $P < 0.001$) were significantly higher in the Target group compared to the control group.

Six patients were screened to have HCC (HCV-related, n = 4; HBV/HCV-coinfected, n = 1; HBV-related, n = 1) in the Target group and none except one had disease awareness for their liver diseases. The patient with disease awareness had HBV/HCV co-infection, but only had awareness of his HBV infection. All 6 patients were referred to receive HCC assessment and treatment consequently. Five HCC patients were Barcelona clinic liver cancer (BCLC) stage A; one was BCLC stage B. Four received curative therapy for HCC (three surgical resection; one radiofrequency ablation); two received trans-arterial chemoembolization (Supplemental Table 1). All five patients with HCV viremia were successfully linked-to-care and achieved SVR12 with DAA therapy. The two patients with HBV viremia received entecavir therapy.

### Characteristics of the subjects with anti-HCV seropositivity between target and control groups

Of the 886 anti-HCV seropositive subjects, the mean age in the Target group was 63.8 years and male accounted for 57.1%, which was similar to those of 194 anti-HCV seropositive subjects in the Control group (Table 2). The HCV viremic rate was similar between the Target group (42.7%, 378/886) and the Control group (41.2%, 80/192). All the

**Table 1** Characteristics and clinical features of the whole subjects among the HCV hyperendemic villages in COMPACT study.

| | Target Group (N = 3684) | Control Group (N = 2047) | P value |
|---|---|---|---|
| Age (years, mean ± SD) | 53.1 ± 15.9 | 50.6 ± 15.1 | <0.001 |
| Male gender, n (%) | 2115 (57.4) | 1220 (59.6) | 0.107 |
| DM, n (%) | 440 (11.9) | 214 (10.5) | 0.089 |
| Hypertension, n (%) | 983 (26.7) | 424 (20.7) | <0.001 |
| BMI, kg/m$^2$ (mean ± SD) | 25.2 ± 4.3 | 24.4 ± 4.2 | <0.001 |
| Uric acid, mg/dL (mean ± SD) | 5.6 ± 1.5 | 5.6 ± 1.6 | 0.063 |
| Triglyceride, mg/dL (mean ± SD) | 123.7 ± 141.0 | 117.2 ± 79.6 | 0.172 |
| Total Cholesterol, mg/dL (mean ± SD) | 194.8 ± 38.5 | 195.4 ± 38.7 | 0.689 |
| Fasting sugar, mg/dL (mean ± SD) | 92.9 ± 34.3 | 89.9 ± 28.8 | 0.015 |
| HbA1c, % (mean ± SD) | 5.9 ± 1.1 | 5.8 ± 0.9 | <0.001 |
| White blood cell count, x10$^3$ u/L (mean ± SD) | 6.4 ± 1.9 | 6.3 ± 1.8 | 0.281 |
| Hemoglobin, g/dL (mean ± SD) | 13.9 ± 1.7 | 13.6 ± 1.8 | <0.001 |
| Platelet count, x10$^3$ u/L (mean ± SD) | 256.2 ± 71.9 | 262.8 ± 70.7 | 0.001 |
| r-GT, IU/L (mean ± SD) | 39.5 ± 75.1 | 32.4 ± 52.4 | <0.001 |
| AST, IU/L (mean ± SD) | 27.7 ± 22.2 | 25.1 ± 16.1 | <0.001 |
| AST >40 IU/L, n (%) | 344 (9.3) | 135 (6.6) | <0.001 |
| ALT, IU/L (mean ± SD) | 29.6 ± 27.6 | 26.1 ± 23.7 | <0.001 |
| ALT >40 IU/L, n (%) | 623 (16.9) | 274 (13.4) | <0.001 |
| α-fetoprotein, ng/ml, (mean ± SD) | 6.4 ± 146.0 | 3.2 ± 14.3 | 0.317 |
| α-fetoprotein >20 ng/ml, n (%) | 31 (0.8) | 10 (0.5) | 0.129 |
| HBsAg (+), n (%) | 378 (10.3) | 171 (8.4) | 0.019 |
| Anti-HCV (+), n (%) | 886 (24.0) | 194 (9.5) | <0.001 |
| HCC at the time of enrollment, n (%) | 6 (0.2) | 0 (0) | <0.001 |

Note: DM: diabetes mellitus. BMI: *Body mass index*. *HbA1c:* Glycohemoglobin A1C. r-GT: gamma glutamyl transferase. AST: aspartate aminotransferase. ALT: alanine aminotransferase. HBsAg: hepatitis B surface antigen. Anti-HCV: hepatitis C antibody. HCC: hepatocellular carcinoma.

other biochemistries and demography did not differ between the two groups except a significantly higher proportion of subjects with liver cirrhosis was observed in Target group (10.8%) than in Control group (4.6%) (P = 0.007).

## Characteristics of the subjects with HCV viremia between target and control group

Of the 378 HCV-viremic subjects in the Target group, the mean age was 62.6 years and males accounted for 59.0%

**Table 2** Characteristics and clinical features of anti-HCV-seropositive subjects among HCV hyperendemic villages in COMPACT study.

| | Target Group (N = 886) | Control Group (N = 194) | P value |
|---|---|---|---|
| Age (years, mean ± SD) | 63.8 ± 11.8 | 62.3 ± 11.4 | 0.104 |
| Male gender, n (%) | 506 (57.1) | 106 (54.6) | 0.529 |
| DM, n (%) | 149 (16.8) | 38 (19.6) | 0.356 |
| Hypertension, n (%) | 358 (40.4) | 76 (39.2) | 0.751 |
| BMI, kg/m$^2$ (mean ± SD) | 25.4 ± 4.0 | 24.8 ± 4.0 | 0.082 |
| Platelet count, x10$^3$ u/L (mean ± SD) | 220.5 ± 66.4 | 222.8 ± 65.0 | 0.663 |
| r-GT, U/L (mean ± SD) | 48.2 ± 106.7 | 39.6 ± 42.2 | 0.272 |
| AST, IU/L (mean ± SD) | 36.5 ± 32.5 | 35.0 ± 32.6 | 0.554 |
| AST >40 IU/L, (%) | 187 (21.1) | 36 (18.6) | 0.427 |
| ALT, IU/L (mean ± SD) | 38.0 ± 40.3 | 38.2 ± 47.7 | 0.946 |
| ALT >40 IU/L, n (%) | 237 (26.7) | 44 (22.7) | 0.242 |
| α-fetoprotein, ng/ml, (mean ± SD) | 16.6 ± 295.6 | 6.4 ± 41.2 | 0.632 |
| α-fetoprotein >20 ng/ml, n (%) | 25 (2.8) | 5 (2.6) | 0.851 |
| HBsAg (+), n (%) | 74 (8.4) | 13 (6.7) | 0.444 |
| HCV RNA (+), n (%) | 378 (42.7) | 80 (41.2) | 0.716 |
| Liver cirrhosis, n (%) | 96 (10.8) | 9 (4.6) | 0.007 |
| HCC at the time of enrollment, n (%) | 5 (0.6) | 0 (0) | <0.001 |

Note: DM: diabetes mellitus. BMI: *Body mass index*. r-GT: gamma glutamyl transferase. AST aspartate aminotransferase. ALT: alanine aminotransferase. HBsAg: hepatitis B surface antigen. HCV: hepatitis C virus. FIB-4: Fibrosis-4 index. HCC: hepatocellular carcinoma.

**Table 3** Characteristics and clinical features of HCV RNA-seropositive subjects among HCV hyperendemic villages in COMPACT study.

| | Target Group (N = 378) | Control Group (N = 80) | P value |
|---|---|---|---|
| Age (years, mean ± SD) | 62.6 ± 12.3 | 60.0 ± 10.8 | 0.073 |
| Male gender, n (%) | 223 (59.0) | 44 (55.0) | 0.51 |
| DM, n (%) | 60 (15.9) | 15 (18.8) | 0.528 |
| Hypertension, n (%) | 159 (42.1) | 26 (32.5) | 0.113 |
| BMI, kg/m$^2$ (mean ± SD) | 25.3 ± 3.8 | 24.2 ± 4.1 | 0.019 |
| Platelet count, x10$^3$ u/L (mean ± SD) | 211.7 ± 69.0 | 222.0 ± 67.0 | 0.224 |
| r-GT, U/L (mean ± SD) | 58.2 ± 105.8 | 52.9 ± 56.7 | 0.662 |
| AST, IU/L (mean ± SD) | 46.8 ± 35.9 | 51.5 ± 45.5 | 0.313 |
| AST >40 IU/L, n (%) | 140 (37.0) | 35 (43.8) | 0.262 |
| ALT, IU/L (mean ± SD) | 52.8 ± 46.6 | 61.7 ± 66.5 | 0.260 |
| ALT >40 IU/L, n (%) | 173 (45.8) | 38 (47.5) | 0.778 |
| α-fetoprotein, ng/ml, (mean ± SD) | 31.1 ± 444.9 | 12.4 ± 63.9 | 0.708 |
| α-fetoprotein >20 ng/ml, n (%) | 22 (5.8) | 5 (6.3) | 0.882 |
| HBsAg (+), n (%) | 25 (6.6) | 4 (5.0) | 0.59 |
| HCV viral loads, log IU/mL (mean ± SD) | 5.5 ± 1.2 | 5.9 ± 1.1 | 0.025 |
| HCV genotype, 1a/1b/(1a+2)/(1 b + 2)/2/3/4/5/6/unclassified/no detected, n (%) | 12/204/2/6/139/0/1/0/8/3/3 (3.2/54.0/0.5/1.6/36.8/0/0.3/0/2.1/0.8/0.8) | 7/37/1/0/32/0/0/0/3/0/0 (8.8/46.3/1.3/0/40.0/0/0/0/3.8/0/0) | |
| Liver cirrhosis, n (%) | 69 (18.3) | 7 (8.8) | 0.046 |
| HCC at the time of enrollment (%) | 5 (1.3) | 0 (0) | <0.001 |

DM: Note: Diabetes mellitus. BMI: *Body mass index*. r-GT: gamma glutamyl transferase. AST: aspartate aminotransferase. ALT: alanine aminotransferase. HBsAg: hepatitis B surface antigen. FIB-4: Fibrosis-4 index. HCC: hepatocellular carcinoma.

(Table 3). The most common viral genotype was HCV-1b (54.0%), followed by HCV-2 (36.8%). The characteristics of HCV-viremic subjects were similar between the Target and Control groups except for a significantly higher BMI (25.3 kg/m$^2$ vs. 24.2 kg/m$^2$, P = 0.019) and a significantly lower HCV RNA levels in the Target group (5.5 logs IU/mL vs. 5.9 logs IU/mL, P = 0.025) and a significantly higher proportion of subjects with liver cirrhosis in Target group (18.3%) than in Control group (8.8%) (P = 0.046). Notably, 211 of 458 (54.9%) HCV viremic subjects had normal ALT levels. All of the 5 anti-HCV positive subjects with HCC found at enrollment were HCV-viremic in the Target group.

## Initial HCV care cascade at the time of enrollment for COMPACT campaign

At initiation of COMPACT engagement, the disease awareness among anti-HCV seropositive subjects was significantly lower in the Target group than in the Control group (53.5% [474/886] vs. 61.9% [120/194], P = 0.034, Table 4). Of the 474 HCV aware subjects in the Target group, 389 (82.1%) subjects had ever got access to medical facilities, which was higher than that of Control group (74.2% [89/120], P = 0.051).

Among assessed subjects in the target group, 215 (66.2%) of 325 need-to-treat subjects had received antivirals (Interferon [IFN]-based regimen: 61.4%, DAAs: 29.8%, IFN followed by DAA: 8.8%) with an SVR rate of 83.3% (n = 179). Among assessed subjects in the control group, 52 (68.4%) of 76 need-to-treat subjects had received antivirals (IFN-based regimen: 44.2%, DAAs: 34.6%, IFN followed by DAA: 21.2%) with an SVR rate of 88.5% (n = 46). Overall, the treatment uptake of need-to-treat subjects was similarly low between the target group (179/557, 32.1%) and the control group (46/126, 36.5%, P = 0.347, Table 4).

Of the 105 cirrhotic patients at initiation of COMPACT engagement, only 58 were aware of HCV infection. Among aware subjects, 44 (75.9%) had access to medical facilities. However, only 11 (28.5%) of 39 need-to-treat cirrhotic patients received antivirals and 9 (81.8%) attained an SVR. To this end, only 9 of the 85 (10.6%) need-to-treat cirrhotic patients achieved an SVR. Similar rates of disease awareness, link-to-care and treatment were observed between cirrhotic Target and Control groups, with an overall treatment uptake among need-to-treat cirrhotic subjects of 10.4% and 12.5% respectively (Table 4).

## HCV care cascade achieved by COMPACT program

We further addressed the HCV care cascade of HCV-viremic patients achieved by COMPACT study engagement (Table 5). Of the 378 HCV-viremic patients in the Target group, 304 (80.4%) were successfully linked-to-care (272 subjects link-to-onsite care; 32 subjects link-to-other sites care), which was significantly higher than that in the control group (70% [56/80], P = 0.039) (51 subjects link-to-onsite care; 5 subjects link-to-other sites care). All of the patients linked-to-care received DAA in both groups. Of the 304 patients who received DAA treatment in the Target group (onsite care: n = 272, other site treaters: n = 32), 3 patients terminated treatment early (one death due to accident; two refused to return) without SVR12 data available, 3 patients lost to follow-up after completing DAA therapy and 2 patients experienced virological relapse (Supplementary

**Table 4** Initial HCV care cascade at the time of enrollment.

| HCV care cascade at enrollment | Total | Target Group | Control Group | P value |
|---|---|---|---|---|
| ***All population*** | | | | |
| | N = 1080 | N = 886 | N = 194 | |
| Anti-HCV awareness in anti-HCV (+) subjects, n (%) | 594 (60.0) | 474 (53.5) | 120 (61.9) | 0.034 |
| - HCV assessed in aware subjects, n/N (%) | 478/594 (80.5) | 389/474 (82.1) | 89/120 (74.2) | 0.051 |
| - HCV being treated in assessed subjects who needed antiviral therapy, n/N[a] (%) | 267/401 (66.6) | 215/325 (66.2) | 52/76 (68.4) | 0.787 |
| - prior anti-HCV regimen, IFN-RBV/DAA/DAA after IFN-RBV. n (%) | 155/82/30 (58.1/30.7/11.2) | 132/64/19 (61.4/29.8/8.8) | 23/18/11 (44.2/34.6/21.2) | |
| - HCV cured at the time of enrollment among treated subjects, n/N (%) | 225/267 (84.3) | 179/215 (83.3) | 46/52 (88.5) | 0.355 |
| Overall treatment uptake among need-to-treat population, n/N[b] (%) | 225/683 (32.9) | 179/557 (32.1) | 46/126 (36.5) | 0.347 |
| ***Subjects with liver cirrhosis*** | | | | |
| | N = 105 | N = 96 | N = 9 | |
| Anti-HCV awareness in anti-HCV (+) subjects, n (%) | 58 (55.2) | 53 (55.2) | 5 (55.6) | 1.00 |
| -HCV assessed in aware subjects, n/N (%) | 44/58 (75.9) | 40/53 (75.5) | 4/5 (80.0) | 1.00 |
| - HCV being treated in assessed subjects who needed antiviral therapy, n/N[a] (%) | 11/39 (28.2) | 10/35 (28.6) | 1/4 (25.0) | 1.00 |
| - prior anti-HCV regimen, IFN-RBV/DAA/DAA after IFN-RBV. n (%) | 9/1/1 (81.8/9.1/9.1) | 9/1/0 (90.0/10.0/0) | 0/0/1 (0/0/100.0) | |
| -HCV cured at the time of enrollment among treated subjects, n/N (%) | 9/11 (81.8) | 8/10 (80.0) | 1/1 (100.0) | 1.00 |
| Overall treatment uptake among need-to-treat population, n/N[b] (%) | 9/85 (10.6) | 8/77 (10.4) | 1/8 (12.5) | 1.00 |

[a] HCV assessed subjects excluding those with spontaneous HCV clearance.
[b] Anti-HCV seropositive subjects excluding those with spontaneous HCV clearance.
Note: HCV: hepatitis C virus. IFN: interferon-based therapy. RBV: ribavirin. DAA: directly acting antivirals.

Fig. 2A). The overall SVR12 rate by ITT and mITT was 97.4% (296/304) and 99.3% (296/298), respectively (Table 5). Of the 56 HCV-viremic patients who received DAA treatment in the Control group (onsite care: n = 51, other sites treater: n = 5), 2 patients terminated treatment early (one death due to subarachnoid hemorrhage unrelated to treatment; one refusal to return) without SVR12 data available (Supplementary Fig. 2B). The overall SVR12 rate by ITT and mITT was 96.4% (54/56) and 100% (54/54), respectively. Taken together, the overall SVR12 rate by ITT and mITT was 97.2% (350/360) and 99.4% (350/352), respectively in the COMPACT study (Table 5). The baseline characteristics and treatment outcome of DAA therapy for HCV-viremic patients treated onsite were listed in Supplemental Table 2. No patients experienced serious adverse events. The characteristics of the 10 subjects who discontinued treatment, lost-to-follow or failed to achieve an SVR were listed in Supplemental Table 3.

Overall, 350 of 458 HCV-viremic subjects were cured by DAA in COMPACT campaign, with community effectiveness of 76.4%. The community effectiveness was significantly higher in Target group than in Control group (78.3%, 296/378 versus 67.5%, 54/80, P = 0.039). The HCV care cascade of Target group after COMPACT campaign was shown in Fig. 1. Taken together, the overall treatment uptake before and after engagement of COMPACT among the need-to-treat population increased from 32.9% to 84.1%; 32.1%—85.1% for Target group and 36.5%—79.4% for Control group.

## Impact of SARS Co—V2 pandemic on the HCV care cascade between target and control groups

To evaluate the impact of the SARS CO—V2 pandemic on the HCV care cascade, we further compared the community effectiveness of HCV elimination between subjects enrolled before (January 2019 to February 2020) and those during (March 2020 to December 2020) the SARS Co—V2 pandemic. A total of 3969 and 1762 subjects were screened in the pre-SARS Co—V2 pandemic period and during the SARS Co—V2 pandemic, respectively, with 348 and 110 subjects seropositive for HCV RNA, respectively (Supplementary Table 4). The rate of successful link-to-care was significantly higher in the pre-SARS Co—V2 pandemic period than during the SARS Co—V2 pandemic period (83.4% vs. 64.5%, P < 0.001). The rates of link-to-treat and SVR12 were comparable between the two groups (100% and 96.9%, respectively, vs. 100% and 95.6% respectively). The

**Table 5** HCV care cascade of the viremic patients after COMPACT study engagement.

| HCV cascade after enrollment | All Subjects (N = 458) | Target Group (N = 378) | Control Group (N = 80) | P value |
|---|---|---|---|---|
| A. Successful link-to-care of HCV viremia subjects, n/N (%) | 360/458 (78.6) | 304/378 (80.4) | 56/80 (70.0) | 0.039 |
| - Successful link-to-onsite care, n/N (%) | 323/458 (70.5) | 272/378 (72.0) | 51/80 (63.8) | 0.14 |
| - Successful link-to-other sites care, n/N (%) | 37/458 (8.1) | 32/378 (8.5) | 5/80 (6.3) | 0.51 |
| B. Successful link-to-treat, n/N (%) | 360/360 (100) | 304/304 (100) | 56/56 (100) | |
| C. Successful antiviral therapy | | | | |
| C1. SVR12 rate, ITT, n/N (%) | 350/360 (97.2) | 296/304 (97.4) | 54/56 (96.4) | 0.66 |
| -SVR12 rate, onsite treatment, ITT, n/N (%) | 313/323 (96.9) | 264/272 (97.1) | 49/51 (96.1) | 0.66 |
| -SVR12 rate, other sites treatment, ITT, n/N (%) | 37/37 (100.0) | 32/32 (100.0) | 5/5 (100.0) | — |
| C2. SVR12 rate, mITT, n/N (%) | 350/352 (99.4) | 296/298 (99.3) | 54/54 (100) | 1 |
| -SVR12 rate, onsite treatment, mITT, n/N (%) | 313/315 (99.4) | 264/266 (99.2) | 49/49 (100.0) | 1 |
| -SVR12 rate, other sites treatment, mITT, n/N (%) | 37/37 (100.0) | 32/32 (100.0) | 5/5 (100.0) | — |
| Community effectiveness in COMPACT[a], n/N (%) | 350/458 (76.4) | 296/378 (78.3) | 54/80 (67.5) | 0.039 |
| Overall treatment uptake[b], n/N (%) | 575/683 (84.1) | 475/557 (85.3) | 100/126 (79.4) | |

[a] Community effectiveness in COMPACT, proportion of HCV cure among HCV-viremic subjects (= A x B x C1).
[b] Overall treatment update, proportion of HCV cure among need-to-treat subjects.
Note: HCV: hepatitis C virus. DAA: directly acting antivirals. SVR12: sustained virological response, defined as undetectable HCV RNA throughout 12 weeks of the post-treatment follow-up period. ITT: intention-to-treat analysis, defined as subjects who had received ≥1 dose of DAA. mITT: modified intention-to-treat analysis, defined as subjects receiving ≥1 dose of DAA and HCV RNA data available at post-treatment week 12.

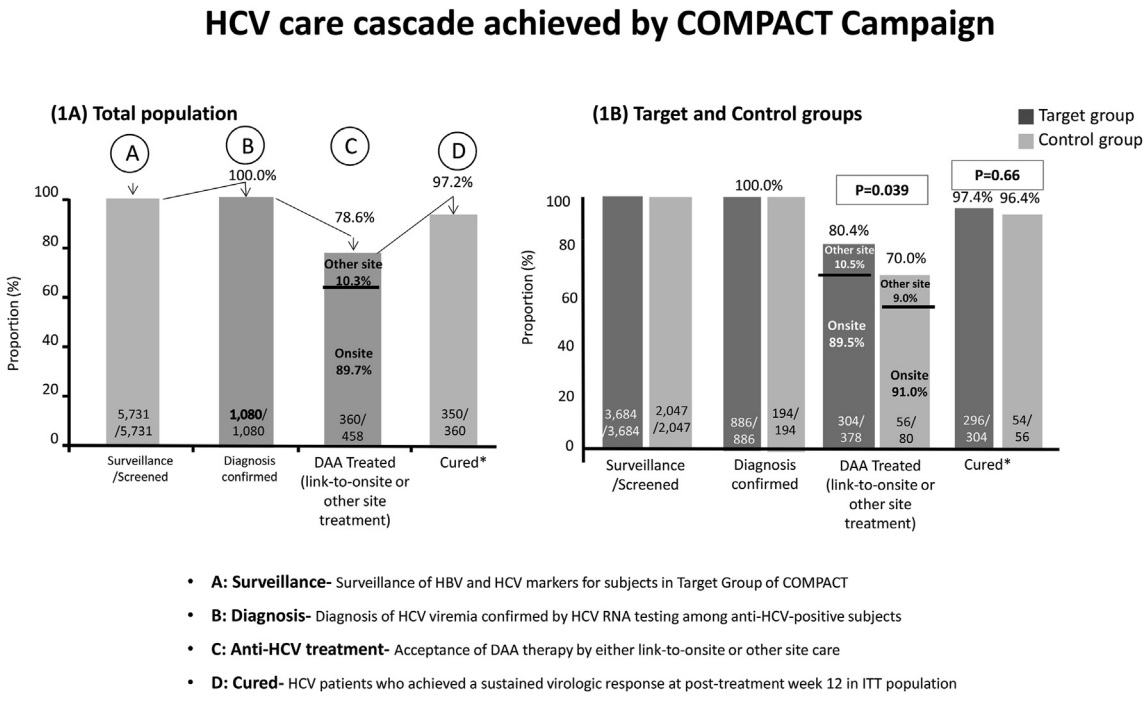


**Figure 1. HCV care cascade achieved by the COMPACT campaign in (A) Total population and (B) Target and Control groups.** EOT: end-of-treatment. SVR: sustained virological response, defined as HCV RNA seronegativity 12 weeks after the end of treatment.

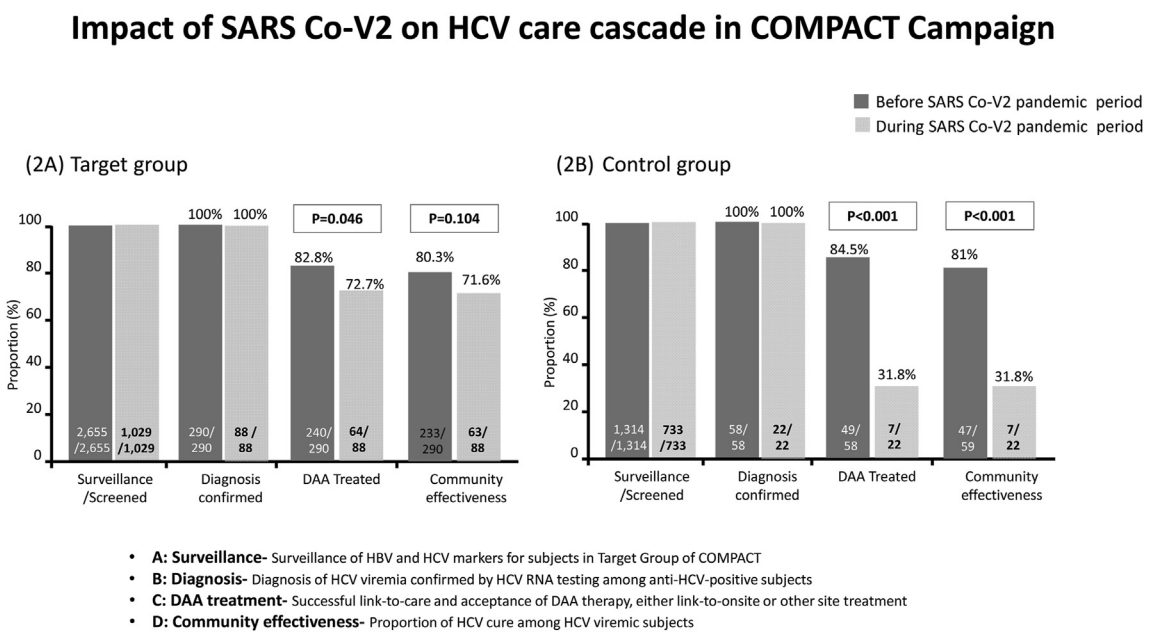


**Figure 2.** HCV care cascades before and during between SARS Co—V2 pandemic in (A) Target group and (B) Control group.

community effectiveness was significantly higher in the pre-SARS Co—V2 pandemic period than during the SARS Co—V2 pandemic period (80.5% vs. 63.6%, $P < 0.001$, Supplementary Table 4).

Among the Target group, 2655 and 1029 subjects were screened in the pre-SARS Co—V2 pandemic period and during the SARS Co—V2 pandemic, respectively, with 290 and 88 HCV-viremic subjects, respectively (Supplementary Table 4). The rate of successful link-to-care was significantly higher in the pre-SARS Co—V2 pandemic period than during the SARS Co—V2 pandemic period (82.8% vs. 72.7%, $P = 0.046$). The rates of link-to-treat and SVR12 were comparable between the two groups (100% and 97.1%, respectively, vs. 100% and 98.4% respectively). Nevertheless, the community effectiveness did not differ between the pre- and during the SARS Co—V2 pandemic periods (80.3% vs. 71.6%, $P = 0.104$, Fig. 2A).

Among the Control group, 1314 and 733 subjects were screened in the pre-SARS Co—V2 pandemic period and during the SARS Co—V2 pandemic, respectively, with 58 and 22 HCV-viremic subjects, respectively (Supplementary Table 4). The rate of successful link-to-care in the pre-SARS Co—V2 pandemic period was 84.5%, which significantly decreased to only 31.8% during the SARS Co—V2 pandemic period ($P < 0.001$). Although the rates of link-to-treat and SVR12 were comparable between the two groups (100% and 95.9%, respectively, vs. 100% and 100% respectively), the community effectiveness decreased significantly from 81% in the pre-SARS Co—V2 pandemic period to only 31.8% during the SARS Co—V2 pandemic period ($P < 0.001$, Fig. 2B).

## Discussion

In the current study, we demonstrated that implementation of a people-centered decentralized outreach program with strategies of "door-by-door" screening followed by an outreach HCV onsite therapy could achieve 80.4% of successful link-to-care, 100% of treatment rate for linked subjects and 97.2% of cured rate for treated patients, with community effectiveness of 78.3% for HCV elimination in a marginalized HCV hyperendemic area, even during COVID-19 pandemic era.

HCV has prevailed in particular in "HCV hyper-endemic townships" such as Tzukuan in Taiwan. As a whole, the seroprevalence of HCV infection has decreased in the past two decades.[24] Similarly, with the continuous efforts implemented by the government and non-government organizations, both the prevalence and incidence of HCV decreased from 21.1% in 2000—2004 to 10.3% in 2015—2019 in Tzukuan.[17] However, the current study revealed that the seroprevalence of anti-HCV remained high in the Target group, 24.0%, indicating there remained hot spots in the HCV hyperendemic area. Since the major risk factor of HCV infection changed from iatrogenic procedures before 2009 to household contact after 2010,[17] "treatment as prevention" has become the key strategy for HCV control in this area.

Despite continuous education in the Tzukuan area during the past decades,[17] only 55% of the anti-HCV seropositive subjects were aware of their HCV infection at the time of enrollment in the current study; the awareness rate was even lower in the Target group than in the Control group. The traditional concept and policy for screening viral hepatitis are only for subjects with abnormal liver function. Compared to a previous hospital-based study in which around 25% of HCV patients had normal ALT levels,[25] more than half of the HCV-viremic subjects had normal ALT levels in the current community-based study. Therefore, the current study used several media strategies and collaborated with local opinion leaders to advocate the importance of universal HCV screening regardless of liver function.

Although the current DAAs provide excellent efficacy and safety profiles, there remains plenty of unmet needs in

eliminating HCV.[26] While the difficult-to-cure population is no longer a critical issue in HCV care, the major hurdle of HCV care exists in properly and accurately identifying the HCV-infected subjects and linking the viremic patients to medical care. To scale up the HCV care cascade, an outreach screen strategy plays a determinant role.[13] Beyond the issue of a novel point of care diagnosis,[27] we first adopted the door-to-door anti-HCV screening followed by HCV RNA reflex testing for those seropositive for ant-HCV.[19] The screen model turned out to have an excellent coverage rate which could serve as an exemplar in HCV care.

Another hurdle for HCV care was the accessibility for patients being diagnosed.[8] The obstacles may arise from the economic barrier and the lack of easy access to the treaters. Before the COMPACT program, around 80% of the aware subjects had HCV assessed before participating in the COMPACT campaign. However, only 66.6% of need-to-treat assessed HCV subjects received antiviral therapy even under the reimbursement of DAA by the National Health Insurance Administration of Taiwan initiated in 2017. The data implicated the importance of providing accessible medical facilities with highly acceptable antiviral regimens to overcome the gap between accessibility and treatment uptake. By adopting the outreach onsite DAA treatment strategy, we provided an excellent treatment rate of 100% for the assessed HCV-viremic patients. The significantly higher rate of link-to-care in the Target group than in the Control group also implied the importance of convenience for accessibility.

As the national insurance fully supports DAAs in Taiwan, the feasibility of medical care would be important, particularly in rural areas. Recently, we successfully set up an outreach onsite treatment model for the uremic population.[14] In the current project, most of the patients linked-to-care were treated by the COMPACT onsite treatment team rather than other clinics. The result successfully replicated the successful experience in the uremic population of the ERASE-C campaign.[14]

All patients linked to medical care were successfully allocated to DAA regimens. Eventually, the community effectiveness of the COMPACT campaign had markedly increased from 32.9% to 76.4% and the treatment uptake of the need-to-treat population from 32.9% to 84.1%. Notably, the community effectiveness was significantly higher in the Target group than in the Control group. Our results proved that a decentralized outreach screening strategy plus onsite treatment service could serve as a model for HCV micro-elimination for marginalized communities with high risk and disease burden of HCV.

Poor awareness of disease severity and lack of apparent symptoms among patients with severe liver diseases are the other challenges urgent for HCV elimination. The current study discovered that one-fifth of the HCV-viremic patients in the Target group had liver cirrhosis at the time of enrollment. In addition, six subjects were identified incidentally with existing HCC, including five HCV-related and one HBV-related in the Target group. All of them were unaware of their liver diseases. The findings reinforce the urgent need for advocating awareness and comprehensive screening of viral hepatitis in the high-risk population. Fortunately, the current DAA regimens are highly effective in HCV eradication for patients with cirrhosis and/or HCC.[28] All of the cirrhotic patients and the five HCV-HCC patients achieved SVR12 after being linked to DAA therapy, except one cirrhotic patient experienced HCV relapsed.

Actually, the COMPACT campaign was affected by the global pandemic of SARS Co—V2 after March 2020,[29,30] resulting in a 6-month delay in completing the project. It is estimated that the pandemic of COVID-19 has markedly impacted the HCV care continuum, in terms of testing access and treatment access.[31] The global impact of a 1-year delay in HCV care has resulted in the loss of HCV treatment and the emergence of new infections, leading to enormous liver-related clinical outcomes.[31,32] Although the COMPACT campaign successfully caught up with the screening target afterward based on the strategies of decentralized onsite service, the SARS Co—V2 pandemic did have an impact on the link-to-care of HCV viremic subjects. However, we demonstrated that the impact of the SARS Co—V2 pandemic was mainly observed in the Control group, but the impact was only minimal in the Target group. The results further emphasized the importance of decentralized onsite services provided in the COMPACT campaign in minimizing the impact of the SARS Co—V2 pandemic on HCV care.

The major societies including US Preventative Services Task Force,[33] Centers for Disease Control and Prevention in US,[34] and American Association for the Study of Liver Diseases—Infectious Diseases Society of America[35] have advocated that rather than baby boomers, all adults should receive universal HCV screening. The universal screen of the adults in the COMPACT has shown that one-fifth of HCV-viremic subjects in the Target Population was with liver cirrhosis and 6 patients presented with HCC at the time of screening. The results reinforce the urgent need of a continuous call for action to HCV elimination.

There are limitations to the outreach model. Firstly, the COMPACT campaign provided service of diagnosis, assessment and treatment for HCV only. Patients have to visit the other clinic to manage their comorbidities if any. Secondly, the outreach teams do not provide sustainable medical services. We found that 7.9% of HCV non-viremic subjects and >20% of HCV-viremic subjects had fibroscan results greater than 12.5 kPa in the community-based study. As HCC remains to occur in the post-SVR era in particular for patients with advanced liver disease, continue surveillance of these patients is warranted.[36,37] How to successfully link the subgroup to long-term monitoring is a challenge after the COMPACT campaign.

In conclusion, HCV remains a major health threat with tremendous gaps in HCV care cascades in the hyperendemic area. The COMPACT campaign, a people-centered, outreach door-by-door screening with outreach decentralized onsite treatment program in collaboration with the health authority and local opinion leaders, greatly improved the HCV diagnosis and accessibility and scaled up the HCV treatment uptake in an HCV hyperendemic area. The strategies have successfully overcome the hurdles of

each HCV care cascade and could serve as a model for HCV elimination in marginalized communities with high-risk populations, even during the pandemic of SARS Co—V2.

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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.2023.04.012.