Research

Caring People of Hepatitis C Carriers Living with Adverse Effects during Antiviral Treatment: A Longitudinal Study

Wen-Nan Chiu[1], Tung-Jung Huang[1], Jiung-Wei Lin[2], Mei-Yen Chen[3-5,†]

Abstract

Aim: To examine the distribution of adverse effects during receiving antiviral treatment (AVT) and neuropsychiatric symptoms and effects of a referral program for hepatitis C virus (HCV) carriers after 5 years.

Background: Although antiviral treatment (AVT) is successful for hepatitis C virus (HCV) infection, there is limited information regarding AVT in liver cancer endemic rural areas. In addition, many patients discontinue treatment because of intolerable adverse effects, including headache, poor appetite, and neuropsychiatric symptoms.

Design: A community-based, prospective cohort study is used.

Methods: This study was a nurse-led health promotion program combined with a multidisciplinary approach for community adults with HCV carriers in southern Taiwan. Six hundred and forty two community adults with HCV carriers participated in this study between August 2011 and July 2016 in collaboration with a local hospital. Assessed parameters included distribution of adverse effects, health-related behaviors, number of treatment completion and decrease in HCV prevalence rate.

Results: The treatment completion and success rates were 76.2% and 75.5%, respectively, although 19% of the participants discontinued treatment because of adverse effects, especially for neuropsychiatric symptoms. During the 5-year follow-up, the prevalence of HCV infection significantly decreased from 20.8% to 11%. Many participants experienced adverse effects, involving six systems, such as influenza-like (80%), and neuropsychiatric symptoms (60.7%), including depressive mood, insomnia, instable emotions, memory degradation, anxiety, and suicide ideation.

Conclusion: The findings highlight the value of a nurse-led referral program for HCV carriers to receive AVT. Thus, healthcare providers should help rural adults overcome the adverse effects, especially for those neuropsychiatric symptoms.

Relevance to clinical practice: The findings suggest that early detection of HCV infection and education of HCV carriers should be a routine part of all general health assessments in endemic areas.

Keywords:

Hepatitis C virus, Antiviral treatment, Adverse effects, Neuropsychiatric symptoms

Background

The hepatitis B virus (HBV) and hepatitis C virus (HCV) are leading causes of liver cirrhosis and hepatocellular carcinoma, and are among the top 10 global causes of death (approximately 1.45 million related deaths each

[1]Department of Internal Medicine, Chang Gung Memorial Hospital, Yunlin, Taiwan

[2]Department of Nursing, Chang Gung Memorial Hospital, Yunlin, Taiwan

[3]Department of Nursing, Chang Gung University of Science and Technology, Chiayi, Taiwan

[4]Department of Nursing, Chang Gung University, Taoyuan, Taiwan

[5]Department of Cardiology, Chang Gung Memorial Hospital, Chiayi, Taiwan

[†]Author for correspondence: Mei-Yen Chen, Department of Nursing, Chang Gung University of Science and Technology, No. 2, Chia-Pu Rd. West Sec., Putz City, Chiayi County 61363, Taiwan , Tel: 886 (5) 3628800, Ext: 2302, Fax: 886-5-3628866; E-mail: meiyen@mail.cgust.edu.tw

year) [1,2]. Although most worldwide infants receive an HBV vaccine, there is no vaccine for HCV, which is a blood-borne virus that is typically transmitted through unsafe injection practices and inadequate sterilization of medical equipment [1]. Approximately 70-80% of people who are infected with HCV will become a chronic carrier, 20% of the infected patients will develop liver cirrhosis, and 3-5% will experience liver cancer [3]. In addition, HCV infection increases the prevalence of carotid atherosclerosis and ischemic heart disease [4,5]), and patients with an HCV infection have a higher mortality rate from both hepatic and non-hepatic diseases, compared to individuals who are anti-HCV seronegative [6]. Fortunately, antiviral therapy (AVT) can cure hepatitis C infection and protect against cardiovascular events [4]; thus, the current standard treatment in Taiwan is combination AVT by using interferon and ribavirin [3].

Hepatitis C is endemic in Taiwan, where liver cirrhosis and hepatocellular carcinoma are the second most common causes of cancer-related deaths, and account for 34.9 deaths per 100,000 persons annually [7]. Although the incidence of HBV infection in Taiwan has declined significantly since 1982, because of mass HBV immunization [8], the national prevalence of HCV remains at 2-4%, and there are 0.6 million carriers in Taiwan [9]. Furthermore, the prevalence is >40% in some rural villages, such as the Mailio and Taishi townships in western coastal Taiwan [10]. This is likely because some rural areas have not had qualified medical personnel and have used unsafe equipment until recently. However, the Taiwan government launched a national health insurance program >20 years ago, and began providing free antiviral treatment in 2003, which includes interferon and ribavirin, for 24-48 weeks to qualified patients who agree to regularly undergo testing to check their serum virological response [3]. Nevertheless, it is difficult to access information regarding HCV, its diagnosis, and its treatment in endemic areas, and many adults still live with acute or chronic HCV infection.

AVT can reduce the incidence of hepatocellular carcinoma [11,12], improve renal and cardiovascular outcomes, and reduce all-cause mortality among patients with end-stage renal disease [13,14]. Studies have also revealed that patients who achieve a virological response by the fourth week of AVT only require 24 weeks of treatment, although patients who are positive for HCV RNA at the fourth week must receive 48 weeks of treatment [9]. The success of AVT is defined as clearance of the virus with a sustained virological response (SVR) after 6 months of treatment completion. Unfortunately, many patients discontinue treatment because of intolerable adverse effects, such as influenza-like symptoms (e.g., fatigue, fever, headache, and poor appetite), neuropsychiatric symptoms (e.g., apathy and depression), or misunderstandings regarding the meaning of their symptoms [15-19]. Moreover, those patients, who have experienced treatment failure without the appropriate care supports, would propagate the misperceptions and rumors regarding the complications of treatment [20]. Consequently, some HCV carriers will not accept AVT. Few studies have explored the adverse effects during AVT in Asian population. Therefore, the present study aimed to explore the adverse effects of AVT, to evaluate the effectiveness of a referral program for hepatitis C carriers to receive AVT, and the effectiveness of a nurse-led health promotion program in areas where liver cancer is endemic.

■ Personalized support and referral program

AVT is successful for HCV infection, and primary healthcare providers play an important role in helping HCV carriers learn about the benefits of AVT and adopt healthy behaviors. The conceptual framework of this study was based on a part of Orem's self-care model [21], as well as health promotion concepts and previous studies regarding liver cancer prevention [10,22]. S**elf-care** is defined as the patient's adoption of learned activities to maintain their health and well-being, and a self-care deficit occurs if the self-care actions do not meet the patient's needs. Thus, healthcare providers have specialized abilities to help people with self-care deficits [21]. To the best of our knowledge, only a few studies have proposed concrete actions to prevent liver cancer at the local level by using a community health-promotion program. In addition, few longitudinal cohort studies have focused on early detection, advocacy, and referral for AVT. Therefore, this study aimed to evaluate an AVT referral program and explore the related adverse effects, unhealthy behaviors, and value of referral services for HCV carriers.

In this context, unhealthy behaviors or conditions that can promote liver cancer include drinking alcohol, betel nut chewing, cigarette smoking,

reduced physical activity, unhealthy eating, and obesity [22]. In addition, maintaining good oral hygiene may reduce the incidence of oral ulcers and enhance medication adherence. Therefore, the researchers promptly provided personalized support to any patient who experienced adverse effects, which included acetaminophen treatment for the patient's symptoms (e.g., headache or fever) and oral hygiene education to help prevent oral ulcers. In addition, the researchers provided verbal encouragement, such as "Congratulations! The treatment is effective for you.", "The more side-effects you have experienced, the better the treatment results will be.", or "The side-effects are temporary, they will disappear when the treatment is completed". Furthermore, the researchers provided spiritual support through encouraging statements, such as "God has excellent arrangements, perhaps he provides you with discipline as a gift." (for Christian participants) or "We are eliminating karmas by struggling with the side-effects, just like experiencing great blessings after disasters." (for Buddhist or Taoist participants).

Methods

■ Design, setting, and participants

A community-based, cross-sectional study was performed between August 2011 and July 2016 in collaboration with a local hospital in areas of the Mailio and Taishi townships, In Taiwan, liver cancer is endemic and most individuals are socioeconomically disadvantaged. This report included 2 phases and used data from an ongoing longitudinal cohort study that is examining a multidisciplinary nurse-led health promotion program. In Taiwan, the Bureau of National Health Insurance provides free physical check-ups every 3 years for adults who are >40 years old. Based on household registration data, the total population of adult residents in 2011 was 47,798 individuals who were living in the 28 villages of both townships. During phase 1 of this study, 6,805 adults (response rate: 14.2%) participated in the free physical check-ups, and 20.8% of these individuals (n=1,405) were HCV-positive [10]. During phase 2, the distributions of adverse effects and adopting health-related behaviors during the AVT were evaluated by using a convenience sampling of the HCV-positive adults who received AVT.

■ Procedures and ethical considerations

The hospital's institutional review board (104-

3495B) approved this study. To encourage participation, the research team called HCV-positive individuals and invited them to undergo an assessment for AVT at the local hospital. All of the consented participants were outpatients over 40 years old with our prior explanation regarding consent form. The research team also disseminated information regarding AVT, its adverse effects, and its benefits through the referral program, and provided personalized support to the participants as necessary. The researchers also provided information regarding the criteria for insurance coverage to all the qualified candidates, and their eligibility were prior confirmed by the research team physicians.

A cover letter was provided with the questionnaires to emphasize that the individuals' responses would be kept confidential. Interviews were performed by using structured and semi-structured questionnaires. The researchers explained the purpose of the study to the participants, who then had an opportunity to review the questionnaires and indicate if they did or did not want to participate.

■ Instruments

Treatment completion and success rates were calculated based on the patients' electronic medical records. Treatment completion was defined as completing 24 or 48 weeks of AVT, and treatment success was defined as a positive SVR after completing treatment.

Prevalence of HCV infection was calculated by using the number of HCV infections divided by the number of adults who lived around two townships and participated in the community-based health check-ups each year [10].

Health-related behaviors were assessed by using 8 questions that were based on experts' recommendations regarding healthy behaviors to prevent liver disease [1,10,18]. Participants were asked "Do you regularly drink alcohol", "Do you smoke cigarettes?", and "Do you chew betel nuts?" The responses were classified as "never" or "current or former user" if the participant currently or previously performed these behaviors. Oral hygiene was assessed by using the following questions: "Do you receive dental check-ups or tooth scaling regularly (every 6 months)?", "Do you brush your teeth after meals at least 2 times every day?", and "Do you use dental floss at least once every day before going to sleep?". Participants who answered "usually/always" were classified as "regular" and

participants that answered "never/ seldom" were classified as "irregular". The participants' diets were assessed by using the following questions: "Do you eat 3 servings of vegetables every day?" and "Do you eat 2 servings of fruit every day?" Responses was classified as "insufficient" if the participant answered "never/sometimes" and as "sufficient" if the participant usually consumed at least 3 servings of vegetables or 2 servings of fruit per day.

Adverse effects were assessed by using a form that was created based on the existing literature [15-17] and the researchers' clinical experience. The assessment form included a checklist of 11 systemic symptoms and 49 items for symptom classification.

Demographic characteristics included age, sex, education level (years of education), marital status, transmission route, comorbidities, body mass index, and living arrangement.

Statistical analysis

All analyses were performed by using SPSS software (version 20; SPSS Inc., Chicago, IL). Demographic data, health-related behaviors, and adverse effects were summarized by using descriptive statistics. Data were presented as number (percentage) for categorical variables and mean ± standard deviation for continuous variables.

Results

The results from phase 1 identified 6,805 rural adults who participated in the first year of the community-based health check-ups **(Figure 1)**. A total of 1,415 individuals were HCV-positive (20.8%) [10], and all of these individuals were invited to visit the local hospital for further evaluation to determine if they were eligible for free AVT. However, some individuals could not be contacted by telephone, and other individuals planned to visit other hospitals. A total of 642 patients were found to be eligible for the free AVT (24-48 weeks of AVT using interferon and ribavirin). The mean age was 59 years (range: 31-73 years), and most of the participants were men (56.5%). The treatment completion rate was 76.2% (n=489) and the treatment success rate was 75.5% (n=352), although 19% of the participants (n=122) discontinued treatment because of complications **(Figure 1)**. During the 5-year follow-up, the prevalence of HCV infection in the community was significantly reduced from 20.8% to 11% **(Figure 2)**.

During phase 2, 112 participants fulfilled the selection criteria and agreed to attend an interview to further explore the distributions of adverse effects and unhealthy behaviors during the AVT. The mean age was 60.5 ± 9.9 years (range: 34-73 years), approximately half of the respondents were women (n=57, 51%), and most respondents had less than a middle-school education (87%) **(Table 1)**. Most respondents were married and living with their family (90%),
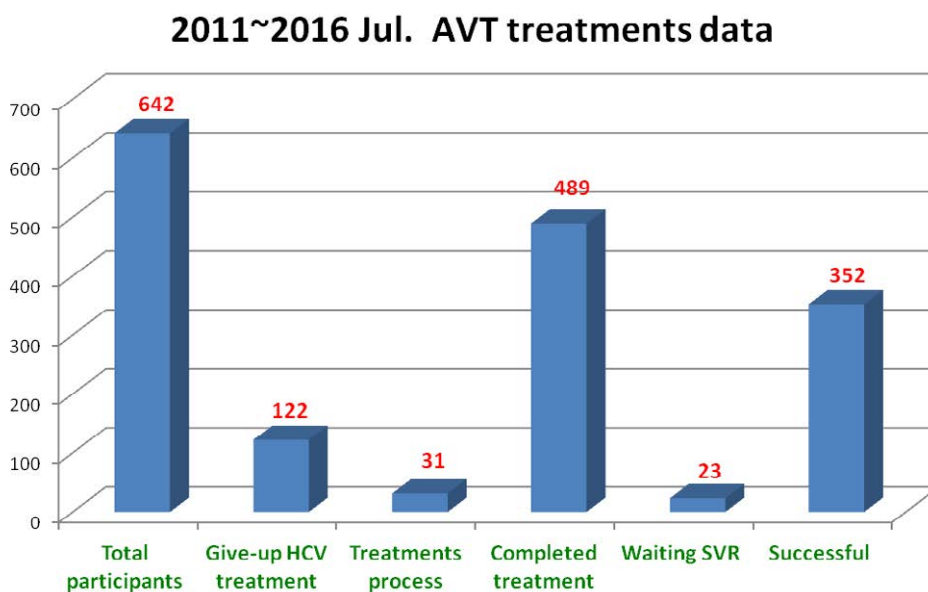
2011~2016 Jul. AVT treatments data

Figure 1: Distribution of AVT treatment data 2011-2016 July.

Figure 2: HCV Prevalence rate based on the community annual health check–ups..

and 65% of the respondents reported that they were not aware of their HCV transmission route. More than half of the respondents reported experiencing comorbidities (55%), which included cardiovascular disease (51%) and diabetes (26%), and most respondents were overweight or obese (77%). More than half of the respondents only had a small number of remaining teeth (59.8%), and 35% of this subgroup had <10 remaining teeth.

While they were receiving AVT, 24% of the respondents reported drinking alcohol, 13% reported chewing betel nuts, and 26% reported smoking **(Table 2)**. Many respondents reported seldom/never receiving regular dental check-ups or tooth scaling (76%), 84% never/seldom brushed their teeth after meals, and 64% never/seldom used dental floss. While receiving AVT, 44% of the respondents consumed an insufficient amount of vegetables and 66% consumed an insufficient amount of fruit.

Many participants who achieved treatment success described being "*grateful and thankful to the nurses and doctors…for giving advice and support during my suffering.*" More than half of the respondents said "*Without their support, I definitely could not go through the bad situation… crying…it's really tough for me…I'm so happy that I have the chance to avoid liver disease… unlike my relatives…I still want to live longer… not like my father… my brother…*" However, most of the respondents who did not achieve treatment success expressed sadness, frustration, and disappointment, and said "*I felt so sad…*

Table 1: Characteristics, health status and treatment outcomes (N=112).	
Characteristics	**N (%)**
Age (years) Mean: 60.5; SD= 9.9; Median=61; Range 34-73	
≤50 yr	18 (16.1)
>51 yr	94 (83.9)
Gender	
Female	57 (50.9)
Male	55 (49.1)
Education level	
Elementary school and below	97 (86.6)
Middle school and above	15 (13.4)
Marital status	
Married	83 (74.1)
Widowed	20 (17.9)
Single	5 (4.5)
Divorced/separated	4 (3.6)
Living arrangement	
Living with families	101 (90.2)
Living alone	8 (7.1)
With others	3 (2.7)
Awareness the HCV transmission route	
Yes	39 (34.8)
Don't know	73 (65.2)
Comorbidities	
Yes	62 (55.4)
No/ don't know	50 (44.6)
Body mass index (BMI) kg/m²	
BMI≦24	26 (23.2)
BMI>24	86 (76.8)
Number of remaining teeth	
<20	67 (59.8)
≧20	45 (40.2)

hopeless…I didn't know what should I do…the process is so hard…I thought I could complete the treatment, but …"

All respondents reported experiencing adverse effects. The adverse effects involved 6 ± 2.9 systems (range: 1-11) and 14 ± 9.9 items (range: 4-43) **(Table 3)**. Most respondents (80%) reported influenza-like symptoms. Other symptoms included skin-related, hair-related, and fingernail-related symptoms (74%); gastrointestinal symptoms (70%); metabolic symptoms (69%); neuropsychiatric symptoms (61%); head, eyes, ears, nose, and mouth symptoms (60%); neuromusculoskeletal symptoms (53%); blood-related symptoms (40%); respiratory symptoms (39%); cardiovascular symptoms (38%), and genitourinary symptoms (23%).

Discussion

The present study revealed four key findings. First, implementing concrete actions (screening for early detection, providing referrals, and offering individual support) was valuable for AVT programs at the local level. Second, the HCV carriers who received AVT were generally older, less educated, and unaware of their transmission route. Third, the participants

reported a wide range of adverse effects (range: 4-43 items). Fourth, many participants adopted unhealthy behaviors while they were receiving AVT.

Studies have revealed that early HCV treatment can stop liver inflammation and prevent cirrhosis. Furthermore, studies in both Europe [23] and Korea [12] have revealed that being <40 years old and having a non-1 genotype were associated with good outcomes, while older age was associated with negative SVR outcomes [9,12]. However, the present study revealed that only 3.6% of the participants were <40 years old when they received AVT. Thus, it is necessary for clinicians and primary healthcare providers to perform early testing to detect HCV, and to encourage HCV carriers to undergo further assessment for AVT.

In addition, rumors and misperceptions in the villages had led many HCV carriers to accept their disease and refuse the free AVT. This might be related to their limited knowledge regarding new AVTs, transmission routes, and access to adequate health services in rural areas. For example, only one-third of the participants reported understanding their transmission route. Furthermore, an American study [24] revealed that stigmatization leads to a lack of support from family and friends during treatment, and that it is easy to discontinue AVT if the patient does not receive adequate support. Therefore, support groups are needed to enhance treatment adherence by encouraging patients to attend or seek counseling.

Previous studies have revealed that achieving a positive SVR leads to significantly more favorable long-term outcomes, which include a lower risk of progression to cirrhosis and hepatocellular carcinoma [12]. Recent studies have also revealed that the treatment success rate is >80–90% if the patient has HCV genotype 2 or 3 [9,12]. We observed a treatment success rate of 75.5%, which is similar to the finding from the World Health Organization (50-90%). Nevertheless, the present study also revealed high rates of discontinuation and a negative SVR, and many participants reported feeling upset, frustrated, and hopeless. Given that genotype 1 is the most prevalent genotype in the Asian population, and that nearly one-third of patients do not experience a good response to AVT, it remains challenging to provide support and hope to these individuals.

The present study also revealed that many

Table 2: Adopting health-related behaviors during antiviral treatment.	
Variables	**N (%)**
Alcohol drinking	
Never	85 (75.9)
Current or former user	27 (24.1)
Betel chewing	
Never	97 (86.6)
Current or former user	15 (13.4)
Cigarette smoking	
Never	83 (74.1)
Current or former user	29 (25.9)
Dental check-ups and tooth scaling	
Regular (half year)	27 (24.1)
Irregular (never/seldom)	85 (75.9)
Brushing teeth after meal	
Regular (usually/always)	18 (16.0)
Irregular (never/seldom)	94 (84.0)
Using dental floss per day	
Regular (usually/always)	40 (35.7)
Irregular (never/seldom)	72 (64.3)
Vegetable (3 servings/per day)	
Sufficient	63 (56.2)
Insufficient	49 (43.8)
Fruit (2 servings/per day)	
Sufficient	38 (33.9)
Insufficient	74 (66.1)

participants adopted unhealthy behaviors while receiving AVT. These unhealthy behaviors (e.g., alcohol consumption, betel nut chewing, and smoking) are risk factors for abnormal liver function, especially among patients with chronic hepatitis [10,23]. In addition, most of the participants did not receive regular tooth scaling and did not regularly brush their teeth or use dental floss after meals. This might have caused adverse oral effects (e.g., oral ulcers, toothache, dry mouth, and gingivitis) and may explain their relatively low number of remaining teeth. The present study also revealed that more than three-quarters of the participants were overweight or obese, and previous studies have indicated that a normal body weight is independently associated with successful AVT, while obesity is associated with liver cancer [25-27]. Although this study did not focus on whether commodities, such as cardiovascular or diabetes associated with side effects during AVT and success rate of treatment. Considering the high prevalence of chronic diseases and overweight appeared in our present study, it is necessary for further studies to explore more comprehensive to understand the factors associated with side effects. For instance patient's pharmacological and chronic diseases history. Moreover, many participants reported having an insufficient intake of vegetables and fruit. Therefore, it is important for primary healthcare providers to initiate health promotion programs that focus on oral hygiene and substance use during AVT, and further studies are needed to explore the link between unhealthy behaviors and HCV clearance.

The adverse effects of AVT involved all physiological and psychological systems. The participants reported 49 unique symptoms, and there was a high prevalence of neuropsychiatric symptoms, such as insomnia, depression, and suicidal ideation. However, a study that used big data from the National Health Insurance Research Database [28] revealed that the risk of non-psychotic mental disorders was only 19.8% higher among patients who were receiving interferon-based therapy. The frequency of adverse effects was also higher in an American study, which revealed that the symptoms included connective tissue disease (37%), abdominal pain (36%), upper respiratory infections (36%), and lower respiratory disease (34%) [29]. Therefore, the high discontinuation rate in the present study might be attributable to treatment-related adverse effects. Furthermore, many HCV carriers reported that their relatives told them that the

	Table 3: Distribution of adverse effects during antiviral treatment.	
	Symptoms by system classification	**N (%)**
1	Influenza-like: e.g. headache, dizzy, exhausted, fever, weak	90 (80.4)
2	Skin,hair and fingernail related: e.g. skin dry, hair loss, rash, nail changes, itching	83 (74.1)
3	Gastrointestinal related: e.g. poor appetite, dysphagia, nausea, vomit,stomach ache, diarrhea, constipation	78 (69.6)
4	Metabolic related e.g. weight loss,weight increase, night sweat	77 (68.8)
5	Neuropsychiatric-related: e.g. depressive mood, insomnia, instable emotions, memory degradation, anxiety, suicide	68 (60.7)
6	Head,eyes,ears,nose and mouth: e.g. changes in vision, photophobia tinnitus, taste change, oral ulcer, tooth ache, dry eyes, sore throat	67 (59.8)
7	Neuro-musculo-skeletal related: e.g. extremites weakness , spasm, joint pain, numbness	59 (52.7)
8	Blood-related: e.g. anemia, easy bruising	45 (40.2)
9	Respiratory related: e.g. cough, dyspnea in activities, phlegmatic, hemoptysis, hard breathing	44 (39.3)
10	Cardiovascular related: e.g. chest tightness,chest pain,palpitations, cold extremities	43 (38.4)
11	Genitourinary related: e.g. micturition,urinary incontinence,nocturnal enuresis,impotence , sexual dysfunction	26 (23.2)

adverse effects might worsen their illness and/ or condition. Moreover, a qualitative Australian study revealed that treatment affected the patients' quality of life and had enormous effects on the social and psychological consequences of living with a highly stigmatized disease that has an unknown course and outcome [30]. Thus, primary healthcare providers can play a significant role in educating patients with chronic hepatitis C and can move beyond the medically oriented approach to care through a deeper understanding of the patient's experiences. Primary healthcare providers can also advocate for patients and help them achieve a reasonable state of well-being [31].

The World Health Organization has acknowledged that population health may achieve the greatest benefits from a social determinants-based approach to policymaking. Thus, it is important to alter the traditional perception of social health determinants among rural HCV carriers [32]. A study by Weiss *et al.* [33] revealed that clear and consistent facilitators could support the local development and implementation of health-promoting policies. Therefore, enhancing concrete actions for local health promotion may help change the course of HCV infection and reduce the incidence of

liver cancer. Further, as the authors from Italy, Ciccone *et al.* [34] suggested that a professional and qualified care manager in the primary health care system should create a strong cooperative and collaborative care "team" to empower the HCV patients for involving more active in their self-care management. The care manager should take responsibility to help HCV patients skill-building and ongoing monitoring to promote their confidence and enhance safety of HCV management at home. Future programs should focus on implementing early-detection and referral systems, and established a care management model to link the physician and HCV patients.

This study has several limitations. Firstly, the small sample size may have led to overestimation or underestimation of the health-related behaviors and adverse effects. Secondly, the participants' responses and the use of questionnaires may have been affected by recall bias. Thirdly, the absence of a control group, potential threats to internal validity of the program needs to be considered. Fourth, the participants were recruited from one rural area with a low socioeconomic status, which potentially limits the generalizability of the findings. Fifth, the qualified and professional care managers are imperatively required in rural hospital. We strongly suggest in the near future, the rural hospital should initial a care management model to collaborate with physicians and HCV patients.

Conclusion

This study aimed to examine the results of a multidisciplinary nurse-led community health-promotion program. The study's findings provide valuable information regarding the effects of a community-based HCV screening and referral system, and personalized support for adverse effects, among HCV carriers who were receiving AVT in disadvantaged areas. Furthermore, the

results suggest that primary healthcare providers can effectively provide information regarding HCV transmission routes, free treatment options, and the benefits of AVT. Moreover, healthcare provides can help address misperceptions and rumors regarding adverse effects from patients who failed treatment; help HCV carriers better understand the relationships between liver disease and being overweight, drinking alcohol, chewing betel nuts, and smoking; and provide additional resources regarding new treatments to patients who have failed treatment.

Ethics Approval

Research Ethics Committee in the Chang Gung Memorial Hospital (104-3495B).

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

WNC and MYC are the principal authors and responsible for the study. TJH are responsible for the data collection. All authors were involved in writing the manuscript and all approved the final version.

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