



# Towards a safe hospital: hepatitis C in-hospital micro-elimination program (HCV-HELP study)

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## Key points

**Question** Is hepatitis C virus (HCV) micro-elimination achievable at the hospital level with the structured strategies?

**Findings** The multidirectional program included the HCV reflex test for hospital personnel, outpatient surveillance, a call-back system, and surveillance of cancer patients prior to chemotherapy. Through the plans of the study, 97.8% of the HCV-viremic patients successfully received linkage-to-treat. The results of each strategy sufficiently met the 2030 elimination goal by the World Health Organization (WHO).

**Meaning** HCV micro-elimination is achievable at the hospital level based on patient safety, staff occupational safety and infection control.

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## Abstract

**Background and aims** Scarce data are available on in-hospital hepatitis C virus (HCV) micro-elimination strategies. This pilot study was prospectively conducted to assess the outcomes of HCV in-hospital micro-elimination program (HCV-HELP) in a single center in Taiwan.

**Methods** The study included the HCV reflex test for plans A (hospital personnel), B (outpatient surveillance), C (a call-back system for anti-HCV+ patients), and D (surveillance of cancer patients prior to chemotherapy). The primary outcome measurement was that > 80% of eligible patients were enrolled in linkage-to-treat; the secondary outcome measurement was the surveillance efficacy.

**Results** We recruited 930, 6072, 2376 and 233 participants into plans A, B, C, and D, respectively, from Oct 2020 to May 2021. The anti-HCV-seropositivity prevalences were 0.22% for plan A, 4.3% for B, and 3.9% for D. Two staff members were identified as HCV-viremic in plan A; these staff members successfully achieved a sustained virological response (SVR). We identified 39, 95 and 2 HCV-viremic patients in plans B, C, and D, respectively. Of these 138 HCV-viremic patients, 135 (97.8%) received direct-acting antiviral therapy, and 134 achieved SVR. Two 4-month phases were stratified to compare efficacies in the liver clinic. In the late phase, the adjusted number of HCV-viremic patients was 4.36/10,000 outpatient visits (90/200,689), which was 3.18-fold higher than that of the early phase (1.37/10,000 outpatient visits [30/212,658], odds ratio 3.18; 95% confidence interval 2.10–4.81,  $p < 0.0001$ ).

**Conclusion** HCV micro-elimination is achievable at the hospital level as per the structured HCV-HELP study.

**Keywords** Hepatitis C virus · Patient safety · Surveillance · Care cascade · Efficacy · Infection control · Micro-elimination · Sustained virological response · Call-back system · Linkage-to-treat

## Abbreviations

HCV	Hepatitis C virus
CHC	Chronic hepatitis C
HCC	Hepatocellular carcinoma
DAAs	Direct-acting antivirals
HCV-HELP	HCV In-Hospital Elimination Program
KMTTH	Kaohsiung Municipal Ta-Tung Hospital
EMR	Electronic medical record
SVR	Sustained virological response
OR	Odds ratio
CI	Confidence interval

## Introduction

Hepatitis C virus (HCV) infection is the leading cause of chronic hepatitis C (CHC), liver cirrhosis and hepatocellular carcinoma (HCC) worldwide [1–4]. The tremendous burden on public health is underestimated mainly because of low disease awareness and the lack of effective preventive measurements [5]. Fortunately, the efficacy and easy dosing of antiviral treatments for CHC are readily accessible for HCV care owing to recently developed direct-acting antivirals (DAAs) [6]. Beyond the issues of blood safety and harm prevention, a thorough HCV care cascade involves properly screening patients who are unaware of their HCV status, accurately and efficiently diagnosing patients, and linking patients to medical care. Additionally, an in-hospital HCV reflex test has been constructed to increase timely and accurate diagnoses, disease awareness and accessibility, followed by automatic

appointments and a late call-back strategy [7]. These strategies help overcome the hurdles to eliminating HCV.

Taiwan has a high prevalence of CHC. The estimated nationwide prevalence is 4%–9%, and the prevalence exceeds 20% in some hyperendemic areas [8]. Along with many achievements in managing HCV, several measurements have been vigorously implemented over the past decade to achieve the ultimate goal of eliminating HCV. These efforts include amelioration of the epidemic in hyperendemic areas and treatment programs for high-risk groups such as CHC patients undergoing dialysis, people who inject drugs, and prisoners [9, 10].

The effectiveness of HCV elimination procedures has been rigorously tested and validated for patients on dialysis because iatrogenic factors are a major mode of HCV transmission in Taiwan. Our recent studies demonstrated that well-designed strategies can effectively ameliorate the hyperendemic state in patients at high risk for HCV [11]. Measurements included efficient confirmational tests, large-scale screening programs, outreach clinics, and easily accessible on-site linkage-to-treat. Nonetheless, a safe hospital environment is necessary to completely eliminate HCV and reduce hazards [12]. Studies reporting this information for in-hospital settings are rare.

Consequently, we conducted this prospective study to assess the efficacy and outcomes of a hospital-based elimination program. The primary outcome measurement was for > 80% of eligible patients to be enrolled in linkage-to-treat; the secondary outcome measurement was surveillance efficacy. The current HCV in-hospital elimination program (HCV-HELP) study was conducted to construct a pilot model for enhancing in-hospital HCV elimination.

## Methods

### Background

Kaohsiung Municipal Ta-Tung Hospital (KMTTH) is located in central Kaohsiung City, Taiwan. It is a core regional hospital established in 2010 and is an affiliated teaching hospital of Kaohsiung Medical University. KMTTH holds 443 beds with a service area of 36,700 m<sup>2</sup> and 968 service staff as of July 2021. KMTTH provides general medical services and treated an average 2200 inpatients/day in 2020.

### Design and strategies

The Institutional Review Board, Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20210009), approved the study, which was conducted in accordance with to the Declaration of Helsinki. The HCV-HELP study included four plans for in-hospital surveillance and elimination: (A) hospital personnel, (B) outpatient surveillance, (C) a call-back system for anti-HCV+ patients based on electronic medical records (EMRs), and D) surveillance of cancer patients prior to chemotherapy (Fig. 1).

#### Plan A. HCV surveillance for hospital staff

All hospital staff have been required to undergo annual health check-ups since 2010 and anti-HCV testing since 2012. Anti-HCV testing is also required for all new staff. Staff who test anti-HCV+ must undergo further HCV RNA testing for confirmation.

#### Plan B. Outpatient surveillance

Plan B provided free anti-HCV testing for outpatients aged  $\geq 40$  years as part of their complimentary annual national health check-up. The HCV care cascade was activated for those who tested anti-HCV+. The cascade mainly included two measurements: (1) HCV reflex testing for increasing timely and accurate diagnoses and (2) real-time automatic liver clinic appointments for improving accessibility. The anti-HCV and/or HCV RNA tests were voluntary.

#### Plan C. Call-back system for anti-HCV+ patients based on their EMRs

A call-back system was implemented by filtering those whose EMR showed that they had been anti-HCV+ since 2010. Patients were excluded if they had histories of undergoing HCV RNA testing or were dead, which was verified by computerized review. The call-back procedures for liver clinic appointments were made by well-trained nursing coordinators using a checklist via phone, mail, texts, email, or app. Successfully contacted patients received HCV RNA tests to confirm their results and assess their treatment.

#### Plan D. Surveillance for cancer patients prior to chemotherapy

A computerized real-time order-entry-based therapeutic control system was introduced in 2011 to remind healthcare

#### b. General population receiving health check-ups

- Free anti-HCV testing
- HCV reflex testing for anti-HCV+ patients
- Real-time automatic liver clinic appointments for HCV RNA+ patients

#### c. Call-back system

- Surveillance of anti-HCV+ patients based on their EMRs
- Call-back procedures for anti-HCV+ patients
- Rechecks of HCV RNA test results
- Real-time automatic liver clinic appointments for HCV RNA+ patients



#### a. Health surveillance for hospital staff

- Free anti-HCV testing during periodic health check-ups
- Free anti-HCV testing for new staff members
- HCV reflex testing for anti-HCV+ staff
- Real-time automatic liver clinic appointments for HCV RNA+ staff

#### d. Surveillance for cancer patients prior to chemotherapy

- Real-time order-entry-based therapeutic control system
- Mandatory anti-HCV testing and reflex testing prior to chemotherapy
- Liver clinic treatment assessment for HCV RNA+ patients

**Fig. 1** Strategies for each plan for in-hospital HCV surveillance and elimination

providers of HBV testing when prescribing chemotherapy. The updated mandatory therapeutic control system for HCV was launched in 2018 when chemotherapeutic agents were prescribed on both inpatient and outpatient bases. Because viral hepatitis infections can be acquired repeatedly, even after initial remission, anti-HCV testing was allowed only within 3 years of the prescription. Anti-HCV data were screened via EMR. The HCV care cascade was activated for anti-HCV+ cancer patients. The cascade included HCV reflex testing and real-time automatic consultations with a hepatologist for vulnerable patients before beginning chemotherapy.

### Laboratory examinations

Anti-HCV tests were performed using second- or third-generation commercially available enzyme-linked immunosorbent assay kits (AxSYM 3.0; Abbott Laboratories, North Chicago, IL, USA). All reactive samples were tested in triplicate and confirmed via HCV RNA assay. Serum HCV RNA was detected using a standardized, automated qualitative reverse-transcription PCR assay (COBAS AMPLICOR Hepatitis C Virus Test, version 2.0; Roche, Branchburg, NJ, USA). All tests were performed in duplicate. The detection limit was 50 IU/mL. The HCV reflex testing procedures were performed for easy-to-access and linkage-to-care purposes. The procedures were previously described [7].

### Statistical analysis

Continuous variables are expressed as the mean  $\pm$  standard deviation. Between-group differences over different time periods were evaluated using the chi-square statistic with the Yates correction or Fisher's exact test. All statistical analyses were based on two-sided hypothesis tests with a

significance level of  $p < 0.05$ . Quality control procedures, database processing, and analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

## Results

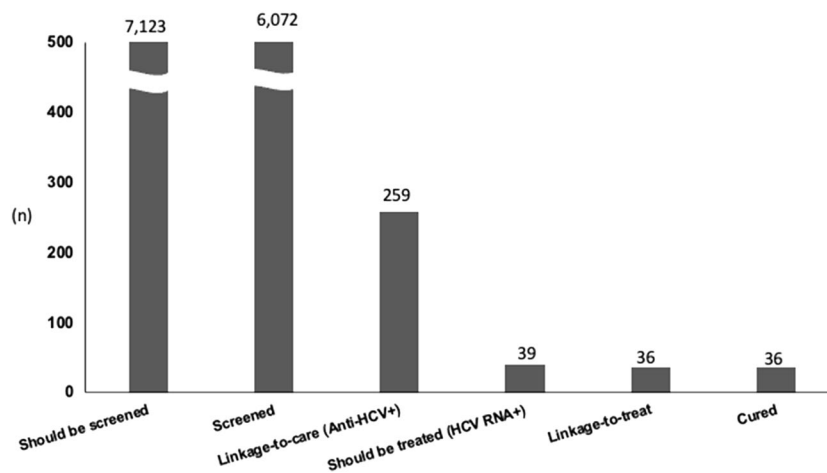
### HCV surveillance for hospital staff

The numbers of registered staff members were 860 in 2016, 870 in 2017, 966 in 2018, 930 in 2019, and 961 in 2020. During their annual health check-ups, two staff members (0.21%) in 2018 and two (0.22%) in 2019 tested seropositive for anti-HCV. No staff tested anti-HCV+ in 2016, 2017, or 2020. The two anti-HCV+ staff members from 2018 tested negative on subsequent reflex HCV RNA testing. The two anti-HCV+ staff members from 2019 tested HCV-viremic on the subsequent reflex HCV RNA testing but have since achieved a sustained virological response (SVR) after undergoing DAA treatment in 2020. Therefore, the goal of having an entirely HCV-free hospital staff was achieved during the study period.

### Outpatient surveillance

Since Oct 2020, we have provided free anti-HCV testing for those aged  $\geq 40$  years at their national annual health check-up. As of May 2021, 6072 of 7123 eligible patients underwent anti-HCV and reflex HCV RNA testing. Of these, 259 (4.3%) were anti-HCV+. Thirty-nine (15.1%) of the 259 anti-HCV+ patients were HCV RNA+, and 36 agreed to further linkage-to-treat arrangements at an outpatient clinic. All 36 patients achieved SVR after DAA treatment. Of the 39 HCV RNA+ patients, 36 (92.3%) were engaged into linkage-to-treat in this plan (Fig. 2).

**Fig. 2** Linkage-to-care cascade for patients undergoing health check-ups



### Call-back system for anti-HCV+ patients based on their EMR

EMR review revealed that 75,424 anti-HCV tests were prescribed, and 4679 anti-HCV+ patients were identified. Of these, 2376 anti-HCV+ patients were included in the call-back pool. Forty-five patients with anti-HCV seroconversion, 2090 patients who had HCV RNA tests prescribed before the call-back procedures, and 168 patients who had died were excluded. Well-trained nursing coordinators performed the call-back procedures via phone, mail, text, email, or app during the study period. They successfully reached 1971 (83%) anti-HCV+ patients, excluding 405 patients who were lost to follow-up after ≥ 3 attempts. Among the 1971 anti-HCV+ patients, 174 (8.8%) were HCV RNA– after assessment, and 691 (35.1%) had received antiviral therapy. Death was confirmed for 191 patients (9.7%), and 228 patients (11.6%) refused treatment despite education. Ninety-five patients (4.8%) HCV RNA+, and all patients received linkage-to-treat. One patient died of a heart attack in week 6 during DAA treatment. The remaining 592 anti-HCV+ patients (30%) who received < 2 notices were assessed for further enrollment in linkage-to-care (Fig. 3).

### Surveillance for cancer patients who received chemotherapy

Seven hundred fifty-six cancer patients received chemotherapy from 2018 to 2020 before the study period. We identified 33 anti-HCV+ cancer patients (4.4%) via the mandatory order-entry-based therapeutic control system. The HCV care cascade was activated for the anti-HCV+ cancer patients, and 25 patients (75.8%) were HCV RNA+. Seven of these HCV RNA+ patients (28%) received DAAs according to

the hepatologist-led HCV treatment consultation before their chemotherapy schedules. The remaining 18 received no HCV treatment because of worsening cancer conditions or refusal. During the study period (Oct 2020 to May 2021), four of 126 cancer patients were identified as anti-HCV+ prior to chemotherapy. Two of these four were HCV RNA+ and were assessed for treatment. One patient successfully eradicated HCV after linkage-to-treat.

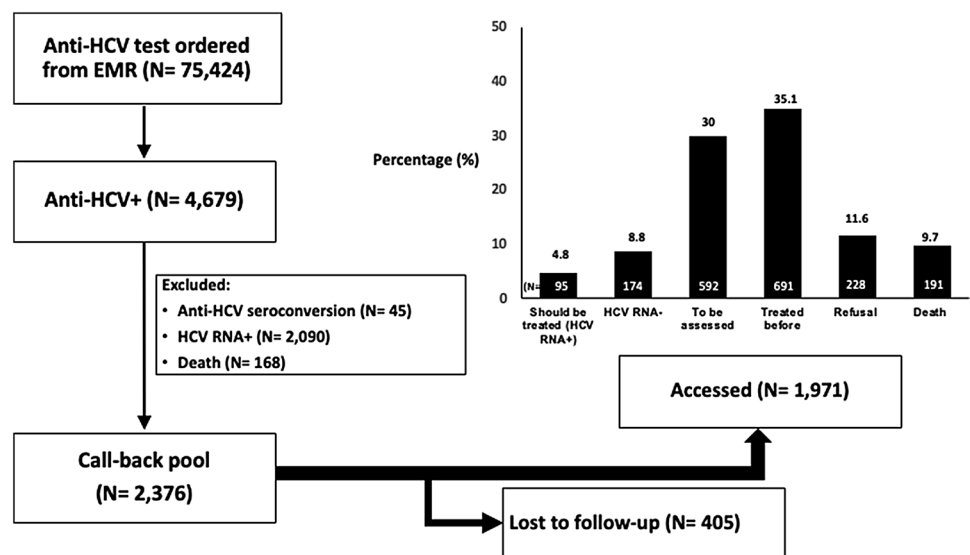
### Care cascade

Through the four plans of the study, 764 anti-HCV+ patients received linkage-to-care, yielding 138 HCV-viremic patients to be treated. Excluding three patients from plan B who refused DAA treatment, 135 were treated and achieved SVR. The primary study outcome, defined as > 80% of eligible patients receiving linkage-to-treat, was thus achieved (97.8%) (Fig. 4). One patient died of a heart attack during DAA treatment, yielding an overall SVR of 99.3%.

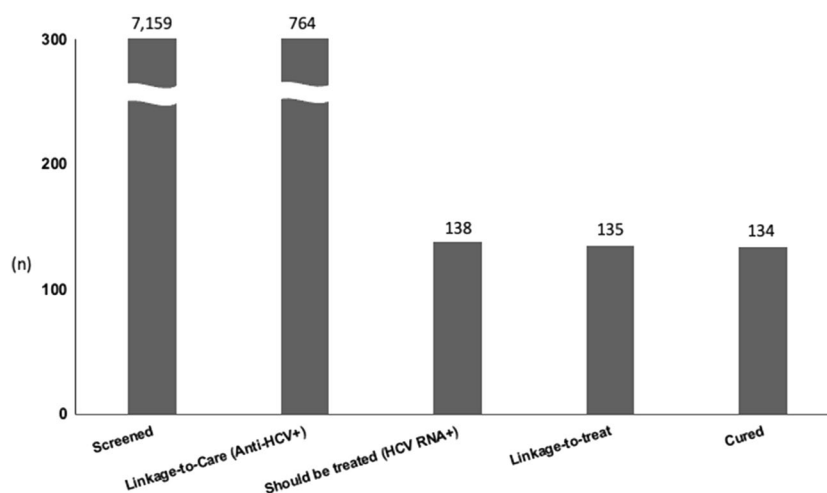
### Efficacy of the surveillance programs with linkage-to-care

The Taiwan Government initiated a free one-time-only HCV screening during annual health check-up since Sep 2020. We, therefore, stratified the HCV-HELP study into two 4-month periods to compare the efficacies of the surveillance programs in the administrative aspect. We assessed the proportion of CHC patients eligible for treatment who received DAAs at our liver clinic. The early phase was Oct 2020–Jan 2021; the late phase was Feb 2021–May 2021. The HCV RNA test results and the HCV RNA+ patients were then adjusted by the total outpatient visits from both phases. The number of prescribed HCV RNA tests performed in the

**Fig. 3** Linkage-to-care cascade for patients identified via the call-back system



**Fig. 4** HCV care cascade in the HCV-HELP study



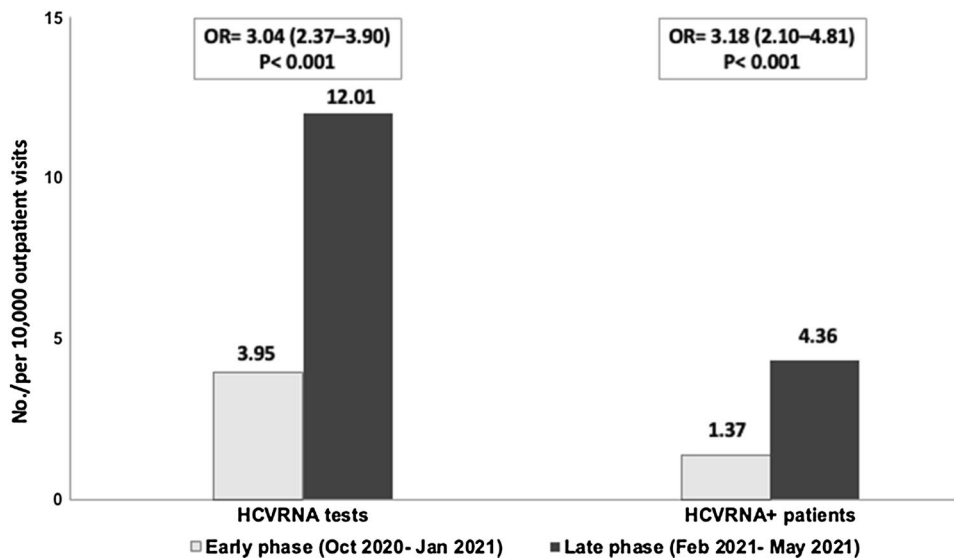
late phase was 12.01/10,000 outpatient visits (241/200,689), which was significantly higher than that performed in the early phase (3.95/10,000 outpatient visits [84/212,658]), yielding an odds ratio (OR) of 3.04 (95% confidence interval [CI]: 2.37–3.90;  $p < 0.0001$ ). In the late phase, the adjusted value of the HCV RNA+ patients was 4.36/10,000 outpatient visits (90/200,689), which was 3.18-fold higher than that of the early phase (1.37/10,000 outpatient visits [30/212,658], OR: 3.18, 95% CI 2.10–4.81,  $p < 0.0001$ ; Fig. 5).

## Discussion

Hospitals should be sterile and safe from infection to meet the health needs of all patients and staff [13]. This study revealed the feasibility and results of an in-hospital comprehensive program for eliminating HCV. To our knowledge, this is the first study to implement multidirectional

strategies to protect a hospital against HCV. We demonstrated that HCV could be completely eliminated among hospital personnel by providing free HCV surveillance for the staff and stringent linkage-to-care monitoring. The strategies for incorporating HCV surveillance into regular nationwide health check-ups for adults enabled recruiting more subjects into linkage-to-care and significantly increased the patients enrolled in linkage-to-treat within a short period. The increase in linkage-to-care patients via the call-back system and entry-based therapeutic control system for cancer patients was mainly attributed to computerized control measurements and well-trained staff. The results of each strategy sufficiently met the 2030 elimination goal by the World Health Organization (WHO). Thus, we successfully reached our goal, resulting in a 3.18-fold increase in HCV RNA+ patients being identified in the late phase of the study compared with that in the early period. Our results, thus, provided a novel model and evidence for an

**Fig. 5** Efficacy of the surveillance programs with linkage-to-care in different phases



in-hospital approach in eliminating HCV. The study also provided insight for implementing public health strategies and well-trained staff.

The overall goal of the WHO Global Health Sector Strategy on Hepatitis (2016–2021) is to eliminate hepatitis as a public health threat within the framework of universal coverage [14]. In recent decades, efforts have been made in public prevention and therapeutic intervention for HCV to achieve this goal [15]. Most previous efforts to eliminate HCV have focused on eliminating HCV infection in terms of disease burden, treatment costs, special populations, and community-based outreach services. Hospital-based elimination strategies, mainly regarding patient safety, staff occupational safety and infection control await further study. Nonetheless, in-hospital elimination is particularly important in Taiwan because iatrogenic factors are the major vehicle for HCV transmission [16–19]. Thus, maintaining a safe environment for HCV infection control and surveilling patients infected with HCV are essential steps toward the goal of eliminating HCV in a hospital-based setting. The HCV-free goal among hospital personnel was achieved within several months in this study. Potential new infections among both new and existing staff members were effectively prevented by annual mandatory health check-ups. This is also essential for reducing occupational hazards.

Disease awareness is a major hurdle for making accurate diagnoses and increasing treatment effectiveness for HCV infections [20]. In 2020, the Taiwanese government instituted free one-time-only HCV screenings during periodic check-ups for those aged 45–79 years [21]. We further extended the screening ages to those aged 40–44 years and those  $\geq 80$  years. These efforts along with implementation of novel health programs have helped raised public disease awareness. Our results echoed those of a previous study showing that the HCV screening rate increased significantly using an EMR notification system within a short period. Konerman et al. demonstrated that 100% of patients newly diagnosed with CHC were referred to specialty care, with 87% having already been seen by a specialist and 67% of those being prescribed DAA therapy [22]. Our study further addressed the success in bridging gaps in linkage-to-care after initial screening as well as a timely diagnosis using the current strategies. Compared with those of the early study period, the number of HCV RNA tests prescribed in the late phase increased by 3.04-fold, and the number of HCV RNA+ patients identified in the late phase increased by 3.18-fold. Moreover, we met the WHO's goal of  $\geq 80\%$  of eligible patients receiving HCV treatment except for those identified via the recall system. Further, follow-up study is needed to assess the long-term efficacy of the current strategies.

A scaling-up of the in-hospital care cascade is important for increasing timely and accurate diagnoses, disease awareness and accessibility. Our recent study in a hospital-based

setting demonstrated that the HCV RNA-testing rate increased significantly in patients who underwent reflex testing [7]. The treatment rate significantly improved for patients from non-hepatology departments, increasing the in-hospital HCV treatment uptake from 6.4 to 73.9% with the strategy [7]. We successfully implemented a diagnostic cascade for special patient groups such as those undergoing dialysis and prisoners [10, 23]. This study further extended the care cascade to vulnerable cancer patients using an entry-based therapeutic control system before initiating chemotherapy. Importantly, patient accessibility may be increased during the COVID-19 pandemic by saving time and reducing the costs of outpatient visits [24].

This study had some limitations. Application of the in-hospital program was mainly an outpatient design. The inpatient section of the hospital may also be a potential reservoir for HCV transmission. Therefore, an add-on inpatient surveillance system has been constructed. Second, the anti-HCV+ patients of the call-back system were excluded if they had histories of undergoing HCV RNA testing because the patients were considered to be linkage-to-care. However, those HCV RNA+ patients might not receive medical care or treatment, particularly in the era of interferon-based therapies. The outcome and the occurrence of linkage-to-care among the HCV RNA+ patients excluded from the call-back system deserved investigation. The limitation might be rescued and validated by information networks between hospital and insurance levels. Third, the study did not cover the invasive procedures in outpatient clinic. Iatrogenic routes of HCV transmission in modern health institutes are largely controlled by staff education, sterile procedures and no-reuse policies for infection control and patient safety. Therefore, the impact may be minimal in this regard.

In conclusion, the study demonstrated the feasibility and efficacy of a comprehensive in-hospital program for eliminating HCV. We demonstrated that the goal of having all hospital personnel be HCV-free was achievable. Strategies for incorporating HCV surveillance into national health check-ups, implementing a call-back system, and activating an entry-based therapeutic control system for cancer patients helped recruit more eligible patients into linkage-to-treat within a short time. Our results, therefore, provide a novel model for an in-hospital approach to the WHO's goal of eliminating HCV.

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**Author contributions** All authors meet the ICMJE criteria for authorship. All authors provided critical review and revision of the text and approved the final version.

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## Declarations

**Conflict of interest** Jee-Fu Huang: Consultant of Roche, BMS, Gilead, Merck, Sysmex, Pharmaessential, Polaris, and Instylla. Speaker for Abbvie, BMS, Gilead, Merck, Sysmex, and Roche. Chia-Yen Dai: Consultant of Abbvie and Roche; Speaker for Abbvie, Gilead, and Roche. Chung-Feng Huang: Speaker for Abbvie, BMS, Bayer, Gilead, Merck, and Roche. Ming-Lung Yu: Research grant from Abbott, BMS, Merck, and Gilead; Consultant of Abbvie, Abbott, Ascleris, BMS, Merck, Gilead, and Roche; Speaker for Abbvie, Abbott, BMS, Merck, Gilead, and IPSEN. Wan-Long Chuang: Consultant of Gilead, Abbvie, BMS, and PharmaEssentia; Speaker for Gilead, Abbvie, BMS, and PharmaEssentia.

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**Manuscript drafting and critical revising** Jee-Fu Huang, Wan-Long Chuang, Ming-Lung Yu, Chung-Feng Huang.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Ethics approval** The study has been approved by Institutional Review Board, Kaohsiung Medical University Hospital (KMUHIRB-E(1)-20210009).

**Data sharing statement** All data relevant to the study are included in the article. Inquiries regarding the datasets used and/or analyzed during this study can be directed to the corresponding authors.

**Consent to participate** The trial was conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. The Institutional Review Board of the Kaohsiung Medical University Hospital approved the analysis of the related data for the study.

**Consent for publication** All authors contributed to the interpretation of the data and reviewed and approved the manuscript.

**Availability of data and material** Authors can confirm that all relevant data are included in the article. We agree with the policy in the journal. The data can be shared (or provided) upon reasonable request.

**Code availability** Not applicable.

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