Clinical Kidney Journal

Clinical Kidney Journal, 2023, vol. 16, no. 12, 2429–2436

https://doi.org/10.1093/ckj/sfad138
Advance Access Publication Date: 14 June 2023
Original Article

ORIGINAL ARTICLE

Therapy as prevention toward HCV elimination in maintenance hemodialysis: a multi-center, prospective cohort study

Chung-Feng Huang [1,2,3,*], Chia-Yen Dai[1,3,*], Chih-Wen Wang[1,4], Po-Cheng Liang[1], Yu-Ju Wei[1,5], Pei-Chien Tsai [1], Tyng-Yuan Jang[1], Po-Yao Hsu[1], Jia-Jung Lee[6], Sheng-Wen Niu[5,6], Jiun-Chi Huang [4,6], Ming-Lun Yeh[1,3], Ching-I Huang[1,3], Ming-Yen Hsieh[1,5], Yi-Hung Lin[1,4], Szu-Chia Chen[4,6], Yi-Wen Chiu[6], Jee-Fu Huang[1,3], Jer-Ming Chang[6], Shang-Jyh Hwang[6], Wan-Long Chuang[1,3] and Ming-Lung Yu [1,3,7,8]; the FORMOSA-LIKE investigators

[1]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [2]PhD Program in Translational Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, and Academia Sinica, Kaohsiung, Taiwan, [3]Faculty of Internal Medicine and Hepatitis Research Center, College of Medicine, and Center for Cohort Study, Kaohsiung Medical University, Kaohsiung, Taiwan, [4]Department of Internal Medicine, Kaohsiung Municipal Siaogang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [5]Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [6]Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [7]School of Medicine, College of Medicine and Center of Excellence for Metabolic Associated Fatty Liver Disease, National Sun Yat-sen University, Kaohsiung, Taiwan and [8]Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

*These authors contributed equally.
Correspondence to: Ming-Lung Yu; E-mail: fish6069@gmail.com, Jer-Ming Chang; E-mail: jemich@cc.kmu.edu.tw

ABSTRACT

Background. The World Health Organization has established interim guidance for hepatitis C virus (HCV) elimination. We aimed to prove the concept of "treatment as prevention" by conducting a prospective HCV elimination program for hemodialysis (HD) patients.

Methods. A universal HCV screen was launched in 22 HD centers in 2019. HCV-viremic patients were linked to care with direct-acting antivirals (DAAs). The second screen was performed in 2021 to evaluate the effect of link-to-care in lowering the prevalence of HCV viremia and the incidence of HCV new/re-infections.

Received: 27.1.2023; Editorial decision: 19.5.2023

Results. Of 2336 patients enrolled in the first screening in 2019, 320 (13.7%) were seropositive for anti-HCV and 181 (7.7%) were HCV-viremic. Of 152 patients successfully linked to treat with DAA, 140 (92.1%) patients achieved a sustained virological response. Of them, 1733 patients participated in the second surveillance. Five anti-HCV-negative patients experienced anti-HCV seroconversion. Of 119 DAA-cured patients and 102 spontaneous HCV clearance patients, none had HCV reinfection. The annual incidence of HCV new infection was 0.1%. Sixty-one of the 620 (9.8%) newly enrolled patients were anti-HCV-seropositive in the second survey. The overall HCV-viremic rate decreased from 7.7% in 2019 to 0.6% (15/2353) in 2021. At the institutional level, 45.5% (10/22) eradicated HCV and 82% (18/22) of HD units had no HCV new infections or reinfections.

Conclusions. The link-to-care project proved the concept of "treatment as prevention" by which HCV microelimination helps to prevent reinfection and new infections in the HD population.

Trial registration: ClinicalTrials.gov identifier: NCT03803410 and NCT03891550.

LAY SUMMARY

This multi-center prospective study demonstrated a drastic reduction in the HCV-viremic rate from 7.7% to 0.6% after 3-year linking to care of HCV microelimination in the hemodialysis population. We further proved the concept of "treatment as prevention," which showed that the rate of HCV primary infection was as low as 0.1%, and none of the HCV-cured patients encountered reinfection.

Keywords: DAA, HCV, hemodialysis, hepacivirus, microelimination

INTRODUCTION

Hepatitis C virus (HCV) infection is recognized as a major global health burden. Patients on maintenance hemodialysis (HD) are at great risk for HCV infection [1]. The prevalence and incidence of HCV infection in end-stage renal disease (ESRD) patients undergoing HD are also high [2, 3]. Taiwan has the leading prevalence and incidence of ESRD worldwide. We previously disclosed that the prevalence of anti-HCV antibody was 13.6% in 2012–18 [3], indicating that HCV remains rampant in the HD population in Taiwan. ESRD patients with HCV infection were more likely to have more comedications and comorbidities than those without HCV infection [4]. HCV-related morbidities and mortalities represent the major disease burden in the ESRD population. ESRD patients with HCV infection are associated with higher risks of cardiovascular disease and hospitalization, worse quality of life and greater mortality [5, 6]. Therefore, there is an urgent need to adopt HCV microelimination among HD patients at both the individual and population levels.

Notably, the updated seroprevalence of HCV infection and HCV care in the era of direct-acting antivirals (DAAs) remain to be addressed. Despite the widespread application of DAAs in Taiwan since 2017, the treatment uptake of DAAs in the HD population remained suboptimal in a recent survey [3]. Poor accessibility due to underlying comorbidities accounted for one of the major hurdles of HCV care in this population [7]. Considered collectively, a comprehensive surveillance program followed by efficient linking to medical care among HD units is warranted.

By launching the ERASE-C Campaign (Establishment of an outreach, grouping health care system to achieve microelimination of HCV for uremic patients in HD centers) in the ESRD on HD population [7], we recently accomplished the primary goal of ≥90% of HCV-infected subjects being diagnosed, ≥80% of whom were being treated by the World Health Organization (WHO) in 2016 [7, 8]. The WHO recently transformed the initial target of a >80% reduction in the incidence of new HCV infection [8] into the absolute indicator of ≤5 per 100 000 new infections/year in the interim guidance [9]. Nevertheless, both goals have rarely been proven during HCV care in the general population or special patient groups. We herein conducted a prospective study by performing two mass screens actively linking HCV-viremic patients to DAA treatment in between. The evolution of HCV prevalence, as well as the incidence of new infection and reinfection rates, was addressed after HCV microelimination in the HD population.

MATERIALS AND METHODS

Patients

The FORMOSA-LIKE Group (the Formosan Coalition for the study of Liver Disease in Chronic Kidney Disease) is a collaborative alliance of hepatologists and nephrologists in southern Taiwan consisting of more than 2000 ESRD patients with maintenance HD in 22 HD units (1 medical center, 4 regional core hospitals and 17 clinics) [3, 7]. The current link-to-care study (L-to-C) prospectively launched the first universal surveillance in January 2019 (initial cohort). All HD patients were tested for anti-HCV antibodies. HCV virology, including viral loads and genotypes, was further tested in patients with anti-HCV seropositivity by the HCV reflex testing algorithm [10]. HCV-viremic patients identified in the first mass screen were introduced to the ERASE-C Campaign between May 2019 and April 2020. Briefly, HCV-viremic patients received onsite treatment by an outreach treatment team or were consequently linked to local DAA treatment [7]. For new patients who joined the FORMOSA-LIKE group for HD later, HCV reflex testing was performed immediately at the time of recruitment. HCV-viremic patients were linked to DAA treatment by local hepatologists according to the HCV guidelines in Taiwan [11–13]. The second surveillance was performed in December 2021, including the both patients who participated in surveillance (longitudinal cohort) and new enrollment in the second surveillance (new cohort). The primary objective was to address HCV seroprevalence before and after L-to-C. The secondary objective was to evaluate the incidence of new HCV infections after L-to-C in the ESRD population per the requirements of the WHO [8, 9]. All patients provided written informed consent. The ethics committee of the Kaohsiung Medical University Hospital approved the study (NCT numbers 03803410 and 03891550).

HCV reinfection was defined as HCV RNA reappearance in the second surveillance for anti-HCV-seropositive/HCV RNA-negative subjects, either due to treatment-induced sustained virological response or to spontaneous clearance. HCV primary infection was defined as anti-HCV seropositivity in the second surveillance that seroconverted from anti-HCV-seronegative subjects in the first surveillance. HCV RNA was retested at a 1-month interval for the newly infected subjects to ensure viremic status. HCV new infection was defined as patients with primary HCV infection or HCV reinfection.

Laboratory testing

Biochemical analyses were performed on a multichannel autoanalyzer (Roche Diagnostics, Mannheim, Germany). Hepatitis B surface antigen (HBsAg) was examined using a standard quantitative chemiluminescent microparticle immunoassay (ARCHITECT HBsAg, Abbott Diagnostics). HCV antibodies were measured by a third-generation enzyme immunoassay (Abbott Laboratories, North Chicago, IL, USA). HCV RNA and genotypes were measured using a real-time PCR assay (RealTime HCV; Abbott Molecular, Des Plaines, IL, USA). Anti-HCV testing is mandatory for each ESRD patient who underwent HD in Taiwan. Anti-HCV-seropositive patients who refused HCV RNA testing were stringently regarded as viremic while judging HCV prevalence. Liver fibrosis was assessed by transient elastography (FibroScan®; Echosens, Paris, France) before DAA treatment. A sustained virological response (SVR12) was defined as HCV RNA seronegativity 12 weeks after the end of DAA treatment.

Statistical analyses

Frequencies were analyzed between groups using the chi-square (χ^2) test with Yates's correction or Fisher's exact test. Group means were calculated as the mean ± standard deviation. The aspartate aminotransferase (AST)-to-platelet ratio index (APRI) was calculated as [(AST level/AST upper limit)/platelet count] × 100. A fibrosis-index 4 (FIB-4) was calculated using the following formula: age (years) × (AST in U/L)/(platelets in 10^9/L) × [alanine transaminase (ALT) in U/L]$^{1/2}$. The treatment efficacy of DAAs was evaluated by intention-to-treat analysis (ITT, all enrolled patients who received one or more dose of DAA) and a modified ITT analysis population (mITT, subjects receiving one or more dose of DAA with HCV RNA data available at posttreatment Week 12, excluding nonvirological failures). Statistical analyses were performed using the SPSS statistical software package, version 20 (SPSS, Chicago, IL, USA). All of the statistical analyses were based on two-sided hypothesis tests with $P < .05$, which indicated statistical significance.

RESULTS

Patient profile in the first surveillance

A total of 2336 patients were enrolled in the first surveillance. The mean age was 64.7 years and females accounted for 47.4% ($n = 1108$). The proportions of the comorbidities were as follows: diabetes (49.7%), hypertension (62.5%), dyslipidemia (29.5%), cerebrovascular disease (10.4%), cardiovascular disease (37.9%) and systemic lupus erythematosus (1.9%). Forty-one (1.8%) patients had a history of hepatocellular carcinoma and 225 had other malignancies (9.6%). The seroprevalences of anti-HCV and HBsAg were 13.7% ($n = 320$) and 11.5% ($n = 268$), respectively. Of the 320 anti-HCV-seropositive patients, 181 (56.6%) were HCV RNA-positive. Of the 139 anti-HCV-seropositive but HCV RNA-negative subjects, 90 patients were due to spontaneous HCV clearance, whereas the remaining 49 patients were due to HCV eradication by prior antiviral therapy (Table 1).

Among the 181 HCV-viremic patients, the mean age was 66.1 years and females accounted for 47.5% ($n = 86$). The mean HCV RNA level was 5.5 log IU/mL. The most common viral genotype was HCV genotype 2 (HCV-2) ($n = 88$, 48.6%), followed by HCV-1 (43.1%, $n = 78$). Twelve patients (6.6%) were dually infected with HBV. The mean values of APRI and FIB-4 were 0.5 and 2.5, respectively. Of the 108 patients with FibroScan data available, the mean value of liver stiffness was 9.4 kPa (Table 2). One hundred and fifty-two (84.0%) patients were linked to DAA treatment, whereas 29 patients refused further antiviral intervention.

DAA treatment responses

Of the 152 patients who received DAA treatment, 140 patients achieved SVR12, 4 patients did not attain SVR12 and 8 patients had no treatment outcome available (7 patients expired and 1 patient was lost to follow-up). Overall, the rate of SVR12 was 92.1% (140/152) by ITT and 97.2% (140/144) by mITT (Fig. 1).

Patient profiles in the second surveillance

In the initial cohort, 332 patients passed away, and 116 patients were transferred out of the FORMOSA-LIKE group for HD before the performing of the second surveillance. After excluding 155 patients who refused the second surveillance or had no data available, 1733 patients in the initial cohort participated in the second surveillance (namely the longitudinal cohort). Compared with the initial cohort, patients in the longitudinal cohort were younger and had smaller proportions of cerebrovascular disease and cardiovascular disease (Fig. 1 and Table 1).

In addition, another 620 new HD patients were enrolled in the FORMOSA-LIKE group during the study period and participated in the second surveillance (new cohort). Compared with the initial cohort, the new cohort was older, had lower levels of AST and ALT, had larger proportions of diabetes and hypertension, and had a smaller proportion of dyslipidemia. The rates of anti-HCV (9.8% vs 13.7%, $P = .01$) and HCV RNA (1.3% vs 7.7%, $P < .001$) in the new cohort were significantly lower than those in the initial cohort (Table 1 and Supplementary data, Fig. S1). Of the 53 anti-HCV-seropositive but HCV RNA-negative patients in the new cohort, 15 were due to spontaneous HCV clearance, whereas the other 38 patients were due to successful HCV eradication by antivirals before entry (Fig. 1b). Considered collectively, the seropositive rate of anti-HCV and HCV RNA viremic rate were 12.4% (292/2353) and 0.6% (15/2353), respectively, in the second surveillance among the combined cohort (longitudinal cohort and new cohort) in 2021 (Table 3). Of the 17 viremic patients identified by the second screen, 6 (4 DAA naïve and 2 DAA experienced) were continually linked to DAA treatment; 3 of them achieved SVR12 (all DAA naïve) (Fig. 1a and b). Ten (45.5%) of the 22 HD centers achieved "No-C HD," defined as a lack of HCV-viremic HD patients or staff members in an HD center [7].

New HCV infection in the longitudinal cohort

Of the 1733 patients in the longitudinal cohort, 5 anti-HCV-seronegative patients became anti-HCV-seropositive in the second surveillance, leading to an annual incidence of HCV primary infections of 0.1%. Of these cases, two were HCV-viremic, whereas the other three had spontaneous HCV RNA clearance.

Table 1: Patient characteristics of initial cohort enrolled in the first surveillance in 2019 and new cohort in 2021.

	Initial cohort, data collected in 2019				
	Total[a] ($n = 2336$)	Longitudinal cohort[b] ($n = 1733$)	*P*-value (a vs b)	New cohort[c], data collected in 2021 ($n = 620$)	*P*-value (a vs c)
Age (years)	64.7 ± 12.3	63.4 ± 11.9	<.001*	66.6 ± 13.2	.001*
Female	1108 (47.4)	850 (49.0)	.31	274 (44.2)	.15
BMI before dialysis (kg/m^2)	24.0 ± 4.4	24.2 ± 4.4	.15	23.9 ± 4.5	.62
HBsAg (+)	268 (11.5)	197 (11.4)	.92	67 (10.8)	.67
Anti-HCV (+)	320 (13.7)	231 (13.3)	.73	61 (9.8)	.01*
HCV RNA (+)	181 (7.7)	124 (7.2)	.48	8 (1.3)	<.001*
WBC (×1000/μL)	6.6 ± 2.2	6.4 ± 2.0	1.00	6.8 ± 2.6	.08
Hemoglobin (g/dL)	10.5 ± 1.6	10.6 ± 1.5	1.00	10.4 ± 1.2	1.00
Platelet count (×1000/μL)	187.2 ± 63.9	187.0 ± 59.9	.92	188.1 ± 66.4	.76
AST (U/L)	19.5 ± 11.2	18.9 ± 9.9	.07	17.9 ± 10.8	.001*
ALT (U/L)	17.3 ± 15.4	16.7 ± 10.8	.14	15.6 ± 11.7	.003*
Albumin (g/dL)	3.9 ± 0.4	4.0 ± 0.3	1.00	3.9 ± 0.4	1.00
Diabetes	1162 (49.7)	816 (47.1)	.09	349 (56.6)	.003*
Hypertension	1460 (62.5)	1059 (61.1)	.38	471 (76.3)	<.001*
Dyslipidemia	689 (29.5)	528 (30.5)	.50	131 (21.2)	<.001*
Cerebrovascular disease	243 (10.4)	148 (8.5)	.05*	70 (11.3)	.51
Cardiovascular disease	885 (37.9)	598 (34.5)	.03*	259 (42.0)	.06
Systemic lupus erythematosus	45 (1.9)	37 (2.1)	.65	6 (1.0)	.12
Hepatocellular carcinoma	41 (1.8)	26 (1.5)	.54	10 (1.6)	.87
Other malignancy	225 (9.6)	167 (9.6)	1.00	48 (7.8)	.18

Data are expressed as mean ± standard deviation or *n* (%).
[a]Initial cohort, patients who participated in first surveillance in 2019.
[b]Longitudinal cohort, patients who participated in both first surveillance in 2019 and second surveillance in 2021.
[c]New patients who participated in the surveillance in 2021.
*Statistical significance.
BMI: body mass index; WBC: white blood cell.

Table 2: Patient characteristics of the 181 HCV-viremic patients enrolled in the first surveillance.

Age (years)	66.1 ± 10.0
Female	86 (47.5)
BMI before dialysis (kg/m^2)	23.5 ± 4.2
BMI after dialysis (kg/m^2)	22.6 ± 4.1
HBsAg (+)	12 (6.6)
HCV RNA, log (IU/mL)	5.5 ± 1.2
HCV genotype (1a/1b/2/6/mixed/unclassified)	5 (2.8)/73 (40.3)/88 (48.6)/12 (6.6)/2 (1.1)/1 (0.6)
WBC (×1000/μL)	6.5 ± 2.2
Hemoglobin (g/dL)	10.5 ± 1.5
Platelet count (×1000/μL)	174.0 ± 66.2
AST (U/L)	27.5 ± 17.7
ALT (U/L)	28.2 ± 31.9
Albumin (g/dL)	3.9 ± 0.4
FIB-4	2.5 ± 2.2
APRI	0.5 ± 0.5
Fibroscan (kPa)[a]	9.4 ± 4.8
Fibroscan >12 kPa[a]	24 (22.2)
Diabetes	105 (58.0)
Hypertension	123 (68.0)
Dyslipidemia	44 (24.3)
Cerebrovascular disease	20 (11.0)
Cardiovascular disease	92 (50.8)
Systemic lupus erythematosus	4 (2.2)
Hepatocellular carcinoma	11 (6.1)
Other malignancy	15 (16.3)

Data are expressed as mean ± standard deviation or *n* (%).
[a]$n = 108$.
BMI: body mass index; kPa: kilopascal; WBC: white blood cell.

As displayed in Table 4, two patients belonged to the same HD unit. The initial seropositive rate of anti-HCV and HCV RNA viremic rate ranged from 9.7% to 22.0% and from 5.6% to 12.0%, respectively, in the four HD units. One patient had been admitted to a hospital for diabetic foot amputation, and the other patient had received dental procedures between the two screenings. None of the five patients had a family history of HCV infection or recent blood transfusion history. Otherwise, no other potential HCV transmission route was identified.

Of the 119 SVR patients and the 102 anti-HCV-seropositive but HCV RNA-negative patients, none had HCV RNA reappearance in the second surveillance, and there was no HCV reinfection (Fig. 1a). We observed that 18 (82%) of the 22 HD centers had no new HCV infections and fulfilled the new goal of the WHO, with ≤5/100 000 new HCV infections.

Evolution of the HCV-viremic rate infection after L-to-C

The HCV-viremic rate was 7.7% (181/2336) on the first screen in 2019. Of the 152 patients who received DAAs, 31 patients did not receive the second screen [23 passed away, 4 were transferred out, and 4 refused rescreening or had no data available (including 3 SVR patients and one non-SVR patient)]. Eventually, 119 SVR patients and 2 non-SVR patients received the second screen, and the viremic status remained consistent with their SVR12 status after DAA treatment. Of the 29 HCV-viremic patients who did not receive DAA treatment, 17 passed away and 7 were transferred out; two patients refused the second screening and were viewed as having persistent viremia. After adding the two new HCV-viremic cases, there remained 10 HCV-viremic patients in the longitudinal cohort. In total, the HCV-viremic rate decreased to 0.6% (10/1733) after executing

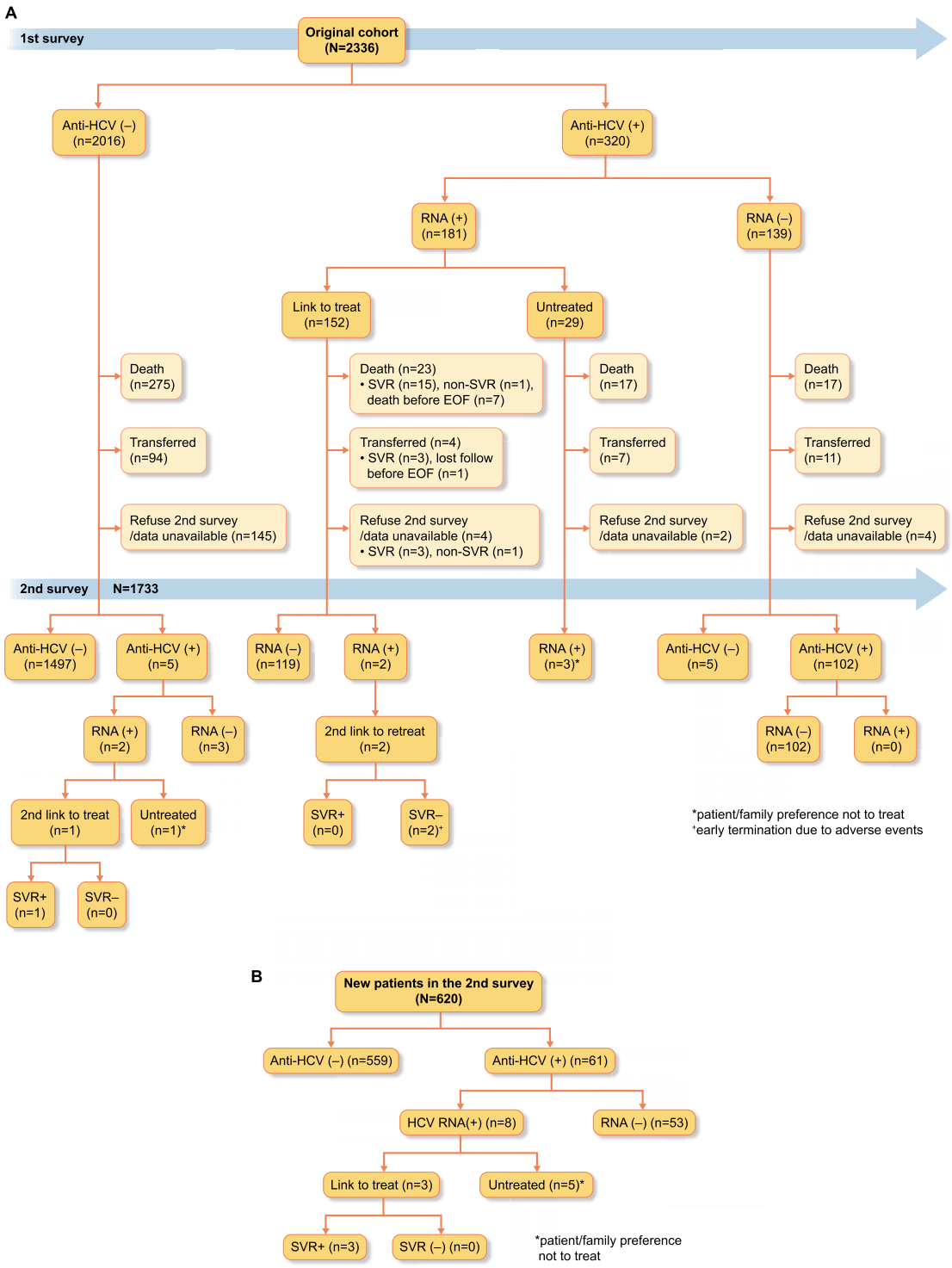

Figure 1: (**A**) Patient flow chart in the original cohort. The first survey took place in 2019, and the second survey took place in 2021. (**B**) Patient flow chart in the new cohort surveyed in 2021.

Table 3: Patients characteristics of the total population participated in the second surveillance in 2021.

	Total ($N = 2353$)
Longitudinal cohort/new cohort (n)	1733/620
Age (years)	65.6 ± 12.3
Female	1 124 (47.8)
BMI before dialysis (kg/m^2)	24.1 ± 4.4
BMI after dialysis (kg/m^2)	23.2 ± 4.3
HBsAg (+), n/N	257/2352 (10.9)
Anti-HCV (+)	292 (12.4)
HCV RNA (+)	15 (0.6)
HCV RNA log (IU/mL)[a]	5.4 ± 1.3
WBC (×1000/μL)	6.6 ± 2.6
Hemoglobin (g/dL)	10.6 ± 1.3
Platelet count (×1000/μL)	184.2 ± 62.5
AST (U/L)	17.6 ± 11.6
ALT (U/L)	15.5 ± 13.0
Albumin (g/dL)	3.9 ± 0.4
Diabetes, n/N	1164/2350 (49.5)
Hypertension, n/N	1533/2350 (65.2)
Dyslipidemia, n/N	658/2350 (28.0)
Cerebrovascular disease, n/N	215/2350 (9.1)
Cardiovascular disease, n/N	856/2350 (36.4)
Systemic lupus erythematosus, n/N	43/2350 (1.8)
Hepatocellular carcinoma, n/N	37/2349 (1.6)
Other malignancy, n/N	217/2349 (9.2)

Data are expressed as mean ± standard deviation or n (%).
[a]$n = 15$.
BMI: body mass index; longitudinal cohort: patients who participated in both first surveillance in 2019 and second surveillance in 2021; WBC: white blood cell.

L-to-C in the longitudinal cohort (Fig. 1a and Supplementary data, Fig. S1b).

DISCUSSION

The current study demonstrated a tremendous reduction in HCV prevalence in the ESRD population after launching the L-to-C project. Through comprehensively decentralized screening followed by timely link-to-treat strategies, we noted a drastic reduction in the HCV-viremic rate from 7.7% to 0.6% as a whole in the FORMOSA-LIKE group. At the institutional level, 10 (45.5%) of the 22 HD centers achieved the "No-C HD" [7]. Moreover, we proved the concept of "treatment as prevention." Given the reduced prevalence of HCV in the environment, the rate of HCV primary infection was as low as 0.1%, and none of the HCV cured patients encountered reinfection.

The World Health Assembly has adopted the Global Health Sector Strategy on the elimination of viral hepatitis by 2030 [8]. However, there remain many barriers to achieving the goal of HCV elimination, including low rates of disease awareness/diagnosis, ineffective linking to care and suboptimal treatment action [14, 15]. In Taiwan, the majority of HD patients did not receive antiviral therapy due to unsatisfactory efficacy and significant adverse events in the interferon era [3]. DAAs have replaced interferon-based therapy as the standard of care in Taiwan since 2017 [12, 13]. The innovation of DAAs provides a very high SVR rate of 95% or more in ESRD patients, as with the general population in the real world in Taiwan [7, 16, 17]. However, the treatment uptake in ESRD patients remains suboptimal in the beginning era of DAAs in Taiwan [3]. The first surveillance of the L-to-C project occurred in early 2019, 2 years after DAA reimbursement in Taiwan. However, the HCV-viremic rate remained as high as 7.7% in the population at the time of screening. Multiple comorbidities and frequent drug–drug interventions in these patients add complexity when approaching this population in the clinical setting [4, 18]. More than half of the anti-HCV-seropositive patients were viremic and remained untreated, indicating the urgent need to promote HCV care in the cohort. After comprehensive outreach screening and consequent linking to care, the viremic rate was drastically reduced to only 0.6%. This result depicted a great reduction in HCV prevalence of >90%, demonstrating successful HCV microelimination in the population.

ESRD patients with HCV infection are associated with a higher risk of morbidities and mortality than those without [5, 19]. Anti-HCV therapy at the patient level may prevent liver-related morbidity/mortality. However, patients remain at risk of contracting HCV as long as viremic patients are left untreated in the HD units, although universal precautions have been strictly adopted [20]. The risk of anti-HCV seroconversion increases with time in HD facilities [1]. Despite the persistent engagement and implementation of the Dialysis Outcomes and Practice Patterns Study, the incidence of HCV infection was 1.2 per 100 patient-years in the participating 21 countries over a long study period from 1996 to 2015 [1]. In Taiwan, the annual incidence of new HCV infection among ESRD patients who underwent maintenance HD was 1.36% in an earlier report [21] and 0.2% between 2012 and 2019 before the widespread application of DAAs [3]. Conversely, a recent report in Taiwan disclosed an HCV annual reinfection rate of 0.23% in HD patients after achieving

Table 4: Characteristics of the five anti-HCV (–) patients who seroconverted to anti-HCV (+).

Case No.	Site number	Age (years)	Sex	anti-HCV titer, S/CO	HCV RNA, IU/mL[a]	Original anti-HCV-seropositive rate in the local site, n/N (%)	Original HCV RNA seropositive rate in the local site, n/N (%)	Family history of HCV	Other potential risk behaviors between the two surveillances
#1	No. 2	55	M	2.71	<LLOD; <LLOD	7/72 (9.7)	4/72 (5.6)	No	Hospitalization for diabetic foot amputation
#2	No. 2	61	M	9.17	0.099; recheck: 0.072	7/72 (9.7)	4/72 (5.6)	No	No
#3	No. 6	63	M	1.21	<LLOD; <LLOD	14/86 (16.3)	10/86 (11.6)	No	No
#4	No. 9	51	F	16.66	361.441; recheck: 177.065	11/50 (22.0)	6/50 (12.0)	No	Dental procedure
#5	No. 10	59	M	1.22	<LLOD; <LLOD	15/122 (12.3)	7/122 (5.7)	No	No

[a]Rechecked 1 month apart for all patients.
M: male; F: female; LLOD: lower limit of detection, 12 IU/mL.

SVR [22]. The latest figures on the prevalence and incidence of HCV in the population in the DAAs era are elusive. The WHO recently issued interim guidance establishing and validating standardized criteria for measuring HCV elimination. One of the goals is to achieve an annual incidence of new infection <5 in 100 000 in the general population [9]. In the current study, we adopted the best method of choice per recommendation by the WHO, which was direct estimation based on a prospective cohort design using HCV antibody retesting of persons who initially tested negative. We further disclosed a new infection rate of only 0.1%/year, and there was no HCV reinfection after executing the HCV microelimination program. Compared with the early report in Taiwan (1.36%/year) [21], a >90% (92.6%) reduction in new infections was achieved using the original WHO goal [8]. At the institutional level, 18 (81.8%) of the 22 facilities had no new HCV infections, achieving the new WHO indicator (≤5/100 000). Although the definite transmission route of the five newly infected HCV patients was obscure, the risk of HCV acquisition is anticipated to be further decreased, accompanied by the resolution of the viral reservoirs in the HD units at the population level. In conclusion, the L-to-C program provided a thorough demonstration of HCV microelimination in the HD population in terms of reducing the HCV prevalence and incidence at the population level. Long-term benefits of HCV eradication in improving hepatic and extrahepatic outcomes on an individual basis are anticipated in vulnerable populations.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

ACKNOWLEDGEMENTS

We thank the members of the Formosan Coalition for the study of Liver Disease in Chronic Kidney Disease (FORMOSA-LIKE group) for their participation: Dr Lii-Jia Yang, Kaohsiung Municipal Cijin Hospital; Dr Ming-Hsing Sung, Hsing-Yi Clinic; Dr Shih-Pi Lin, Lenity Clinic; Dr Fei-Ching Li, Yu-Sheng Clinic; Dr Jheng-Tai Shien, Chung-Ching Clinic; Dr Chen-Hung Shih, Wu-Fu Clinic; Dr June-Ming Yang, June-Ming Clinic; Dr Cheng-Hsueh Lee, Ming-Gang Clinic; Dr Yi-Cheng Chen, Shih-Chuan Clinic; Dr Yen-Chao Wang, Gang-Shan Clinic; Dr Meng-Chang Yang, Park Medicines Clinic; Dr June-Tse Yang, Dr Kang-Kuei Lin, Yung-Ho General Hospital; Dr Pei-Ing Kong, Yong-Ding Clinic; Dr Hsuan-Sheng Chuang, Shun-Tai Clinic; Dr Gi-Gin Wu, Shin-Kao Hospital; Dr Shih-Meng Yeh, You-Zhen Clinic; Dr Tung-Chang Chuang, People Clinic, Dr Ying-Chih Lin, Ping-Tung Hospital; and Dr Pei-Hua Yu, Wen-Hsiung Hospital. The authors thank the Taiwan Liver Research Foundation (TLRF) for its administrative assistance. The funding did not influence how the study was conducted or the approval of the manuscript.

FUNDING

This study was supported partly by grants from Kaohsiung Medical University (MOST 108-2314-B-037-066 -MY3, MOST 108-2314-B-037-003) and Kaohsiung Medical University Hospital [KMUH-DK(整)109005~1, KMUH-DK(世)109002, KMUH-DK(C)110011, KMUH-DK(C)111006, KMU-DK(B)111002-1, KMUH-DK(C)110004, KMUH-DK(C)111004, KMUH-DK(B)111003-2, KMUH109-9R07]. This study was also supported in part by research grants from the Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp. (MISP#58122) and Gilead Science (IN-TW-342-5567). The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp. or Gilead Science.

AUTHORS' CONTRIBUTIONS

Conception and design: M.-L.Yu. Acquisition of data: C.-Y.D.; C.-W.W.; P.-C.L.; Y.-J.W.; P.-C.T.; T.-Y.J.; P.-Y.H.; J.-J.L.; S.-W.N.; J.-C.H.; M.-L.Yeh; C.-IH.; M.-Y.H.; Y.-H.L.; S.-C.C.; J.-F.H.; Y.-W.C.; J.-M.C.; S.-J.H., and W.-L.C. Data analysis and interpretation: C.-F.H. and M.-L.Yu. Manuscript drafting and critical revision: C.-F.H. and M.-L.Yu. Approval of the final version of the manuscript: M.-L.Yu.

DATA AVAILABILITY STATEMENT

The data would be available with the permits of the corresponding authors.

CONFLICT OF INTEREST STATEMENT

M.-L.Yu.: research support from AbbVie, Abbott, BMS, Gilead, Merck and Roche. Consultant for AbbVie, Abbott, Ascletis, BMS, Gilead, J&J, Merck, Novartis, Pharmaessential and Roche. Speaker for AbbVie, Abbott, Ascletis, BMS, Gilead, Merck, Pharmaessential and Roche. C.-F.H.: speaker for AbbVie, BMS, Gilead, Merck and Roche.

REFERENCES

1. Jadoul M, Bieber BA, Martin P *et al*. Prevalence, incidence, and risk factors for hepatitis C virus infection in hemodialysis patients. *Kidney Int* 2019;**95**:939–47. https://doi.org/10.1016/j.kint.2018.11.038
2. Yu ML, Dai CY, Huang CF *et al*. High hepatitis B virus surface antigen levels and favorable interleukin 28B genotype predict spontaneous hepatitis C virus clearance in uremic patients. *J Hepatol* 2014;**60**:253–9. https://doi.org/10.1016/j.jhep.2013.09.023
3. Wei YJ, Hsu PY, Lee JJ *et al*. Evolutionary seroepidemiology of viral hepatitis and the gap in hepatitis C care cascades among uraemic patients receiving haemodialysis in Taiwan-the Formosa-Like Group. *J Viral Hepat* 2021;**28**:719–27. https://doi.org/10.1111/jvh.13477
4. Hsu PY, Wei YJ, Liang PC *et al*. Comorbidities in patients with chronic hepatitis C and hepatitis B on hemodialysis. *J Gastroenterol Hepatol* 2021;**36**:2261–9. https://doi.org/10.1111/jgh.15480
5. Fabrizi F, Dixit V, Messa P. Hepatitis C virus and mortality among patients on dialysis: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2019;**43**:244–54. https://doi.org/10.1016/j.clinre.2018.10.009
6. Goodkin DA, Bieber B, Jadoul M *et al*. Mortality, hospitalization, and quality of life among patients with hepatitis C infection on hemodialysis. *Clin J Am Soc Nephrol* 2017;**12**:287–97. https://doi.org/10.2215/CJN.07940716
7. Yu ML, Huang CF, Wei YJ *et al*. Establishment of an outreach, grouping healthcare system to achieve microelimination of HCV for uremic patients in haemodialysis centres (ERASE-C). *Gut* 2021;**70**:2349–58. https://doi.org/10.1136/gutjnl-2020-323277

8. World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. 2016. https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf
9. Interim guidance for country validation of viral hepatitis elimination. https://wwwwhoint/publications/i/item/9789240028395 (24 April 2022, date last accessed).
10. Huang CF, Wu PF, Yeh ML *et al*. Scaling up the in-hospital hepatitis C virus care cascade in Taiwan. *Clin Mol Hepatol* 2021;**27**:136–43. https://doi.org/10.3350/cmh.2020.0150
11. Huang CF, Tseng KC, Cheng PN *et al*. Impact of sofosbuvir-based direct-acting antivirals on renal function in chronic hepatitis C patients with impaired renal function: a large cohort study from the nationwide HCV Registry Program (TACR). *Clin Gastroenterol Hepatol* 2022;**20**:1151–62.e6. https://doi.org/10.1016/j.cgh.2021.07.037
12. Yu ML, Chen PJ, Dai CY *et al*. 2020 Taiwan consensus statement on the management of hepatitis C: part (I) general population. *J Formos Med Assoc* 2020;**119**:1019–40. https://doi.org/10.1016/j.jfma.2020.04.003
13. Yu ML, Chen PJ, Dai CY *et al*. 2020 Taiwan consensus statement on the management of hepatitis C: part (II) special populations. *J Formos Med Assoc* 2020;**119**:1135–57. https://doi.org/10.1016/j.jfma.2020.04.002
14. Yu ML, Yeh ML, Tsai PC *et al*. Huge gap between clinical efficacy and community effectiveness in the treatment of chronic hepatitis C: a nationwide survey in Taiwan. *Medicine (Baltimore)* 2015;**94**:e690. https://doi.org/10.1097/MD.0000000000000690
15. Tsai PC, Dai CY, Huang CI *et al*. Low disease awareness as a contributing factor to the high prevalence of hepatitis C infection in Tzukuan, a hyperendemic area of southern Taiwan. *Kaohsiung J Med Sci* 2022;**38**:694–702. https://doi.org/10.1002/kjm2.12552
16. Huang CF, Chiu YW, Yu ML. Patient-centered outreach treatment toward micro-elimination of hepatitis C virus infection in hemodialysis patients. *Kidney Int* 2020;**97**:421. https://doi.org/10.1016/j.kint.2019.10.030
17. Liu CH, Chen CY, Su WW *et al*. Sofosbuvir/velpatasvir with or without low-dose ribavirin for patients with chronic hepatitis C virus infection and severe renal impairment. *Gut* 2022;**71**:176–84. https://doi.org/10.1136/gutjnl-2020-323569
18. Hsu PY, Wei YJ, Lee JJ *et al*. Comedications and potential drug-drug interactions with direct-acting antivirals in hepatitis C patients on hemodialysis. *Clin Mol Hepatol* 2021;**27**:186–96. https://doi.org/10.3350/cmh.2020.0180
19. Fabrizi F, Dixit V, Messa P *et al*. Hepatitis C-related liver disease in dialysis patients. *Contrib Nephrol* 2012;**176**:42–53. https://doi.org/10.1159/000332379
20. Martin P, Awan AA, Berenguer MC *et al*. Executive Summary of the KDIGO 2022 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease. *Kidney Int* 2022;**102**:1228–37. https://doi.org/10.1016/j.kint.2022.07.012
21. Liu CH, Kao JH. Treatment of hepatitis C virus infection in patients with end-stage renal disease. *J Gastroenterol Hepatol* 2011;**26**:228–39. https://doi.org/10.1111/j.1440-1746.2010.06488.x
22. Liu CH, Peng CY, Kao WY *et al*. Hepatitis C virus reinfection in patients on haemodialysis after achieving sustained virologic response with antiviral treatment. *Aliment Pharmacol Ther* 2022;**55**:434–45.