Hepatology Research

WILEY JSH

ORIGINAL ARTICLE OPEN ACCESS

Community-Based Micro-Elimination of Hepatitis C Virus in a Defined Rural Cohort: Outcomes From the Nagawa Project

Hiroyuki Kobayashi[1,2] | Masao Ota[1,2] | Katsuhiko Matsuzaki[3] | Hiromi Yamada[3] | Daiki Aomura[2,4] | Nao Joshita[5] | Hajime Midorikawa[6] | Takayuki Nimura[6] | Kosuke Yamaka[2,4] | Yukifumi Kurasawa[6] | Kazuhiro Suyama[6] | Hiromichi Misawa[7] | Satoru Joshita[2,6,8,9]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Shinshu University School of Medicine, Matsumoto, Japan | [2]Department of Health Promotion Medicine, Shinshu University School of Medicine, Matsumoto, Japan | [3]Department of Clinical Laboratory, National Health Insurance Yodakubo Hospital, Nagawa, Japan | [4]Department of Nephrology, Shinshu University School of Medicine, Matsumoto, Japan | [5]Health Care Center, National Health Insurance Yodakubo Hospital, Nagawa, Japan | [6]Department of Internal Medicine, National Health Insurance Yodakubo Hospital, Nagawa, Japan | [7]Spine Center, National Health Insurance Yodakubo Hospital, Nagawa, Japan | [8]Department of Internal Medicine, Matsumoto Dental University, Shiojiri, Japan | [9]Department of Active Ageing, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Correspondence: Satoru Joshita (joshita@yodakubo-hp.jp)

Received: 13 May 2025 | **Revised:** 30 July 2025 | **Accepted:** 5 August 2025

Funding: The authors sincerely appreciate the research support provided in part by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant-in-Aid for Challenging Exploratory Research (23K18561) and for Scientific Research (C) (25K11171).

Keywords: cohort-based screening | direct-acting antivirals | hepatitis C virus | micro-elimination | rural healthcare

ABSTRACT

Background and Aims: Hepatitis C virus (HCV) infection remains a global public health concern, with many carriers remaining undiagnosed because of its asymptomatic nature. Although Japan was previously considered to be on track for national HCV elimination by 2030, recent global modeling studies and updated elimination dashboards indicate that Japan is currently not on track. This underscores the importance of locally coordinated efforts to detect residual cases. Micro-elimination has recently emerged as a pragmatic and scalable approach by targeting defined populations or geographic areas. The Nagawa Project sought to identify HCV positive individuals through community-wide screening and directing viremic cases to appropriate direct-acting antiviral (DAA) therapy. The present study describes the implementation and outcomes of this cohort-based HCV micro-elimination strategy.

Methods: All 5027 adult residents of Nagawa town, Japan, aged ≥ 20 years were prospectively targeted for HCV antibody testing through routine health check-ups, outpatient visits, and mailed invitations between June 2021 and March 2024. HCV Antibody positive individuals underwent additional HCV core antigen testing to confirm viremia.

Results: A total of 3121 residents (62.1%) underwent HCV antibody testing. Testing rates were significantly higher in early-stage elderly (65–74 years; 73.7%) residents than in both adult (20–64 years; 54.5%) ($p < 0.001$) and late-stage elderly (≥ 75 years; 66.7%) ($p < 0.001$) residents. Twenty-eight individuals (0.897%) were HCV antibody positive, with three cases (0.096%) confirmed as viremic. Antibody positivity was significantly higher in late-stage elderly residents (1.91%; $p < 0.001$ vs. adult and $p = 0.031$ vs. early-stage elderly residents). Two viremic individuals received DAA therapy and achieved a sustained

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; DAA, direct-acting antiviral; GLE/PIB, glecaprevir/pibrentasvir; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HCVAb, hepatitis C virus antibody; HIV, human immunodeficiency virus; HT, hypertension; ICM, ischemic cardiomyopathy; M2BPGi, Mac-2 binding protein glycosylation isomer; NHI, National Health Insurance; SVR, sustained virological response; T1DM, type 1 diabetes mellitus; UMIN, University Hospital Medical Information Network.

virological response. After adjusting for age and sex by propensity score matching, no significant difference in overall survival was observed between HCV antibody positive and negative individuals.

Conclusion: The Nagawa Project illustrates the success of a locally coordinated HCV micro-elimination approach. It offers a practical framework for identifying and managing residual HCV infections, contributing to progress toward Japan's alignment with the World Health Organization's 2030 HCV elimination goals.

1 | Introduction

Hepatitis C virus (HCV) infection may progress to a chronic state, leading to hepatitis progression, liver cirrhosis, and ultimately hepatocellular carcinoma (HCC) [1]. In recent years, the introduction of direct-acting antivirals (DAAs) has revolutionized HCV treatment in clinical practice by achieving a virtually 100% sustained virological response (SVR) regardless of older age, history of HCC, and other risk factors [2, 3]. As many infected carriers remain asymptomatic, however, identifying HCV positive cases remains a public health challenge. Accurate diagnosis through blood testing and appropriate linkage to treatment are essential steps toward effective disease eradication.

The World Health Organization (WHO) set goals for global HCV elimination in 2016, outlining a 65% decrease in HCV mortality and 80% reduction in new HCV infections by 2030 to avert a reported 1.5 million deaths from HCV viremia [4, 5]. However, achieving these targets requires a massive upscale in testing and treatment efforts to reach the estimated 71 million people living with HCV worldwide [6]. It is estimated that 750,000 to 1,250,000 individuals carry HCV antibodies in Japan [7]. Accordingly, the Basic Act on Hepatitis Control was enacted in 2009, under which local governments have offered hepatitis screening as a part of health promotion programs for residents aged ≥ 40 years and prefectural authorities have conducted additional screening as part of infectious disease control policies [7]. Although Japan made substantial progress in HCV control and was previously considered to be on track for elimination by 2030 [8], recent global assessments suggest that Japan is currently not on track [9]. In particular, gaps in diagnosis and treatment remain, in particular among older adults [10], highlighting the need for novel and regionally adapted screening strategies.

The micro-elimination strategy has recently been introduced as a pragmatic and scalable approach to accelerate HCV elimination. This method targets specific high-risk populations, such as those with past parenteral exposure, defined birth cohorts, and individuals receiving chronic care, instead of conventional blanket population-wide screening [11–14]. In other words, micro-elimination divides the broader goal of HCV elimination into smaller more achievable targets to address disparities in HCV awareness and treatment access [15]. However, evidence on the implementation and outcomes of cohort-based HCV micro-elimination remains scarce.

Located in the Chiisagata district of Nagano Prefecture, Nagawa town (population: 5903 as of September 1, 2020) has coordinated comprehensive health check-up initiatives since 1972 under the direction of the municipal Health and Welfare Division. The town provides biennial health screenings, alternating between a full medical "Ningen Dock" examination and metabolic syndrome-specific check-ups under financial support from the local government. The National Health Insurance (NHI) Yodakubo Hospital conducts all such check-ups as the town's only public medical facility and offers routine outpatient care for chronic diseases. Given its integrated health infrastructure and high resident participation, Nagawa town provides an ideal setting for a cohort-based HCV micro-elimination project.

2 | Patients and Methods

2.1 | Target Population

The study flowchart of the Nagawa Project is presented in Figure 1. A total of 5027 residents of Nagawa town aged ≥ 20 years as of April 1, 2021, were initially targeted as candidates for HCV antibody testing in this prospective analysis. For residents who underwent a health check-up or visited an outpatient clinic at NHI Yodakubo hospital, serum samples from any blood testing were temporarily stored for HCV antibody analysis between June 2021 and March 2024. To enhance the participation rate of HCV antibody testing, invitation letters to undergo HCV antibody testing were sent between June 2023 and October 2023 to individual residents who did not receive a health check-up or outpatient consultation as of May 31, 2023. Residents requesting HCV antibody testing were scheduled for blood sampling at NHI Yodakubo hospital on Monday and Wednesday afternoons every week, as well as on 2 Saturdays or Sundays each month, between June 2023 and March 2024.

2.2 | Public Awareness Campaign on HCV Testing

Public awareness programs to inform residents on HCV testing followed a 3-pronged approach. First, notice of the tests and a column on liver disease were published in the town's monthly newsletter. Second, residents were informed that HCV testing was being conducted through the town's wired broadcast system at the beginning of each month. Third, news of the testing program was spread through text broadcasts on the town's cable TV channel.

2.3 | Measurement of HCV Antibody and Definition of HCV Antibody Positivity

A serum HCV antibody (HISCL-HCVAb; Sysmex Co., Kobe, Japan) was measured using a HISCL-5000 fully automated

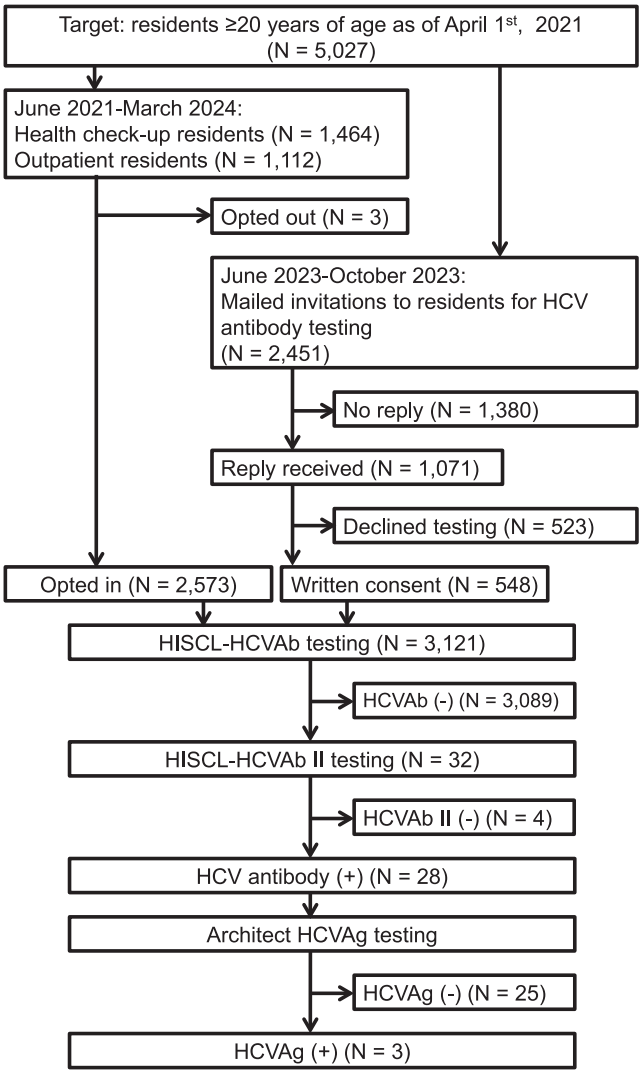

FIGURE 1 | Schematic flowchart of the Nagawa Project study. HCV, hepatitis C virus and HCVAb, hepatitis C virus antibody.

CLEIA device (Sysmex Co.). When a positive HISCL-HCVAb result of > 1.0 C.O.I. was encountered, HISCL-HCVAb II (Sysmex Co.) was measured next. Concurrent positivity of HISCL-HCVAb II at > 1.0 C.O.I. was defined as HCV antibody positive. Positive HISCL-HCVAb but negative HISCL-HCVAb II was judged as HCV antibody negative (i.e., HISCL-HCVAb false-positive).

2.4 | Determination of HCV Viremia in HCV Antibody Positive Individuals

HCV core antigen (Architect HCVAg; Abbott Japan LLC, Tokyo, Japan) was measured by outsourced testing using remaining serum samples to confirm viremia as HCV antibodies could also be positive in HCV clearance residents. Architect HCVAg ≥ 3.0 fmol/L was defined as positive. Ultimately, residents with both HCV antibody and HCV core antigen positive samples were defined as HCV viremia patients, with those being HCV antibody positive but HCV core antigen negative judged as HCV clearance patients.

2.5 | Notification of HCV Antibody Testing Result to Residents

The HCV antibody testing results were sent to participants by mail within 2 weeks after measurement. For residents with HCV viremia, a note was included recommending medical consultation for the possibility of HCV infection. For HCV clearance patients, the letter stated that HCV viremia was unlikely; however, a medical consultation was recommended for those whose history of HCV treatment was unclear, those who had never undergone a detailed examination, and those with any concerns. Residents who tested negative for HCV antibody were informed that they had no evidence of HCV infection.

2.6 | Comparisons of HCV Antibody Testing Rates and HCV Antibody Positivity Rates According to Age Group

The HCV antibody testing rates and HCV antibody positivity rates in adult (20–64 years old), early-stage elderly (65–74 years old), and late-stage elderly (75+ years old) residents using the Chi-squared test.

2.7 | Clinical Comparisons of HCV Antibody Positive and Negative Residents

Age and gender were compared between the HCV antibody positive and HCV antibody negative cohorts. To evaluate the independent association between HCV antibody positivity and prognosis, we used propensity score matching to adjust for baseline confounding factors. Age and sex were significantly associated both with HCV antibody positivity and with survival outcomes, and were therefore included as covariates in the propensity score model. Propensity scores were estimated using a logistic regression model, with HCV antibody status as the dependent variable and age and sex as independent variables. Based on these scores, each HCV antibody positive patient was matched to three HCV antibody negative patients (1:3 matching) using nearest-neighbor matching without replacement. A caliper width of 0.2 standard deviations of the logit of the propensity score was used, in accordance with established guidelines to ensure optimal covariate balance. Survival outcomes in the matched cohort were analyzed using Kaplan–Meier survival curves and compared using the log-rank test, with June 1, 2021—the start of testing—as the baseline. Survival and death were monitored through March 2025 to include a 1-year follow-up period after the conclusion of testing in March 2024.

2.8 | Comparisons of HCV Antibody Testing Rates and HCV Antibody Positivity Rates by Area Within Nagawa Town

Nagawa town is divided into four areas: the town center area of the Furumachi district, the surrounding area of the Nagakubo district, the mountainous area of the Daimon district, and the Wada village area, which had been merged from a former administrative district. HCV antibody testing rates and HCV

positivity rates were compared among these regions using the Chi-squared test.

2.9 | Funding for HCV Testing

HCV antibody testing was conducted with the free provision of test reagents through joint research with Sysmex Co. HCV core antigen was measured using funds from the research budget of the Department of Health Promotion Medicine. Therefore, all procedures were free for participating residents.

2.10 | Ethics

This study was reviewed and approved by the Institutional Review Board of Shinshu University School of Medicine (no. 4992). All researchers involved in this study conducted the investigation in accordance with the Declaration of Helsinki (revised in 2013 by Fortaleza) and the Ethical Guidelines for Medical Research Involving Human Subjects (partially revised on February 28, 2017). An opt-out system is in place at NHI Yodakubo Hospital, Nagawa town, and Shinshu University School of Medicine. All information on the protocol and conduct of the study, including its purpose, is available on the Department of Medicine, Shinshu University School of Medicine website (http://www.shinshu-u.ac.jp/faculty/medicine/chair/i-2nai/). Patients who did not wish to participate in the research were freely able to opt out of the study. Written informed consent was obtained from residents indicating a desire for testing from mailings upon arrival at NHI Yodakubo hospital for blood sampling. This study was partly registered as UMIN 000044114 on May 6, 2021 [16].

3 | Results

3.1 | Number of Residents Receiving HCV Antibody Testing

Of the 5027 adults aged ≥ 20 years who were eligible for HCV antibody testing in Nagawa town, 1464 residents underwent a comprehensive medical check-up and 1112 residents received outpatient treatment for chronic conditions, resulting in 2573 serum samples being analyzed after excluding 3 residents who opted out during this process (Table 1, Figure 1). Of the 2451 individually mailed residents, 1071 replied, yielding a 43.7% response rate. Among them, 523 residents did not want HCV antibody testing, whereas 548 residents elected for testing after providing written informed consent. Ultimately, 3121 individuals received HCV antibody analysis, resulting in a 62.1% cohort-based HCV testing rate (Figure 2a).

3.2 | HCV Antibody Testing According to Age Group

The HCV antibody testing rates in adult, early-stage elderly, and late-stage elderly residents were 54.5%, 73.7%, and 66.7%, respectively (Figure 2a). The early-stage elderly group had a

TABLE 1 | Comparisons of HCV antibody testing rates and HCV antibody positivity rates by areas within Nagawa town.

	Furumachi	Nagakubo	Daimon	Wada	*p* value
Population (N)[b]	1572	1020	998	1437	
HCV antibody testing residents (N)	970	633	598	850	
HCV antibody testing rate (%)	61.7	62.1	59.9	59.2	0.368[a]
HCV antibody positive residents (N)	10	7	2	9	
HCV antibody positivity rate (%)	1.03	1.11	0.33	1.06	0.422[a]

Abbreviation: HCV, hepatitis C virus.
[a]A total of 70 residents were excluded from this regional analysis due to relocation or death during the observation period.
[b]Percentages across regions were compared using the chi-square test.

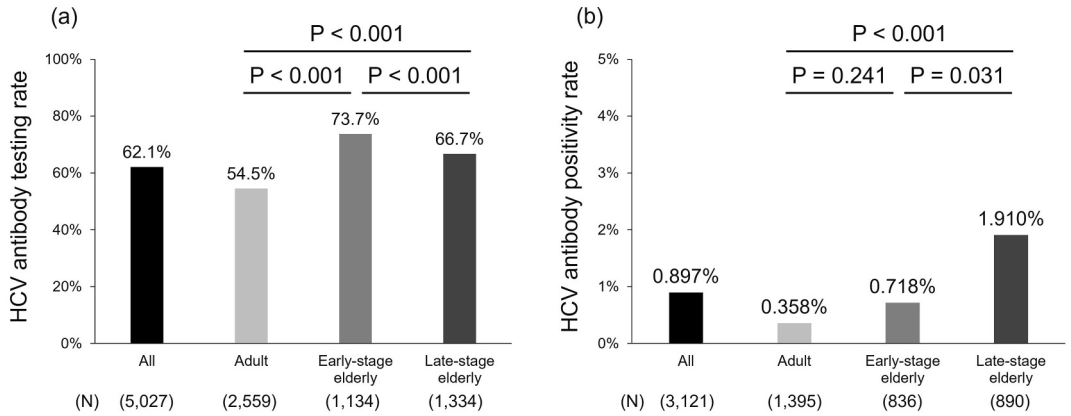

FIGURE 2 | (a) Comparisons of HCV antibody testing rates and (b) HCV antibody positivity rates among adult (20–64 years old), early-stage elderly (65–74 years old), and late-stage elderly (75+ years old) residents. HCV, hepatitis C virus.

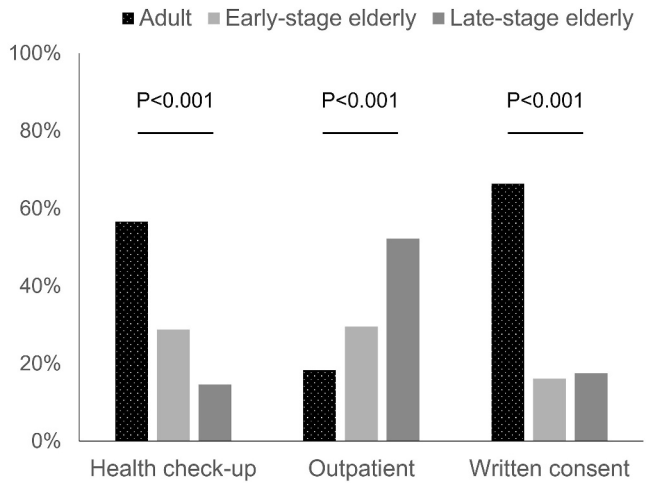

FIGURE 3 | Distribution of HCV antibody testing methods by age group. The proportion of tested individuals in each testing category (health check-up, outpatient, and written consent) stratified by age group was depicted. Adults were more likely to respond through written consent, early-stage elderly residents mostly underwent testing during health check-ups, and outpatient visits were the predominant route in the late-stage elderly resident group.

significantly higher HCV antibody testing rate compared with the other groups (both $P < 0.001$) (Figure 2a).

Furthermore, the method of participation varied across age groups. Health check-up testing was most frequent among adults, outpatient testing increased with age, and written consent was more common in adult group (Figure 3).

The HCV antibody positivity rate was 0.897% (28/3121 residents) among all participants. The respective HCV antibody positivity rates in adult, early-stage elderly, and late-stage elderly residents were 0.358%, 0.718%, and 1.910%. The HCV antibody positivity rate was significantly higher in the late-stage elderly group than in the adult ($P < 0.001$) and early-stage elderly ($P = 0.031$) groups (Figure 2b).

3.3 | Clinical Comparisons Between HCV Antibody Positive and Negative Groups

The HCV antibody positive group was significantly older than the HCV antibody negative group (median age: 77 vs. 67 years; $P < 0.001$). Female gender was also significantly more prevalent in the HCV antibody positive group (71.4% vs. 51.7%; $P = 0.037$). A propensity score matching analysis based on age and sex successfully balanced the baseline characteristics between the HCV antibody–positive and –negative groups. After matching, no statistically significant difference in overall survival was observed between the two groups (Figure 4).

3.4 | Comparisons of HCV Antibody Testing by Area Within Nagawa Town

The HCV antibody testing rates in Furumachi, Nagakubo, Daimon, and Wada were 61.7%, 62.1%, 59.9%, and 59.2%,

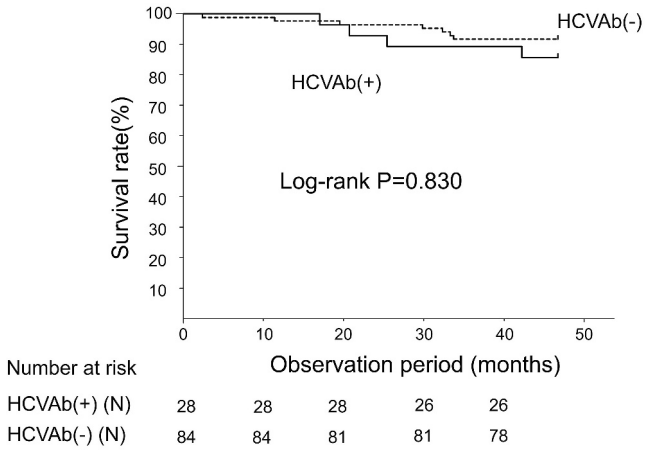

FIGURE 4 | Comparisons of survival rates between HCV antibody positive and negative residents after adjusting for age and sex by propensity score matching. HCV, hepatitis C virus and HCVAb, HCV antibody.

respectively (Table 1). No significant differences were detected for HCV antibody testing rates among these areas ($P = 0.368$). The respective HCV antibody positivity rates in Furumachi, Nagakubo, Daimon, and Wada were 1.03%, 1.11%, 0.33%, and 1.06%, which were also statistically comparable ($P = 0.422$).

3.5 | HCV Antibody Positive Residents

Among the 28 identified HCV antibody positive residents, 25 were defined as having HCV clearance, whereas 3 were judged as harboring HCV viremia by HCV core antigen measurement. Fifteen of the HCV clearance residents were confirmed to have achieved an SVR based on medical history. The remaining 10 residents were considered to have a possible history of HCV, including acute hepatitis C infection, or may have been pseudo-positive for HCV antibody. Subsequent clinical follow-up with HCV RNA testing of the three residents who tested positive for HCV core antigen confirmed their status as HCV carriers, indicating an HCV carrier rate of 0.096% (3/3121 residents).

3.6 | Characteristics of Residents With HCV Viremia

The clinical characteristics of the three newly identified HCV carriers are summarized in Table 2. Case 1 was a 94-year-old man with serotype 1 HCV infection and concurrent hepatitis B virus coinfection. His alanine aminotransferase (ALT) level was within normal range at 15 U/L. Because of his advanced age and diminished performance status, he declined DAA therapy, opting instead for follow-up observation. Case 2 was a 56-year-old male patient who, according to retrospective history taking, had previously been pointed out as having HCV antibody positivity but had remained untreated. He was found to harbor serotype 2 HCV infection. Laboratory tests revealed an elevated ALT level of 104 U/L and increased Mac-2 binding protein glycosylation isomer (M2BPGi) level, leading to a diagnosis of chronic active hepatitis. Subsequent treatment with glecaprevir/pibrentasvir (GLE/PIB) successfully achieved an SVR. Case 3

TABLE 2 | Clinical characteristics of newly identified HCV carriers.

	Case 1	Case 2	Case 3
Age (years)	94	56	53
Gender	Male	Male	Female
ALT (U/L)	15	104	17
AST (U/L)	21	88	23
Albumin (g/dL)	2.8	4.3	4.3
Platelet count (/μL)	161,000	162,000	286,000
M2BPGi (C.O.I.)	1.53	3.06	0.36
Autotaxin	1.530	1.481	0.599
HCVAb (C.O.I.)	82.3	118.3	83.3
HCV core antigen (fmol/L)	5640.0	92.5	13300.0
HCV RNA (log IU/mL)	6.0	1.7	7.3
Serotype	1	2	Indeterminate
Co-infection (HBV or HIV)	HBV	None	None
DAA therapy	No	GLE/PIB	GLE/PIB
DAA therapy outcome	—	SVR	SVR
Comorbidities	HT, CKD, ICM, chronic subcutaneous hematoma	T1DM, HT	HT

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; DAA, direct-acting antiviral; GLE/PIB, glecaprevir/pibrentasvir; HBV, hepatitis B virus; HCV, hepatitis C virus; HCVAb, hepatitis C virus antibody; HIV, human immunodeficiency virus; HT, hypertension; ICM, ischemic cardiomyopathy; M2BPGi, Mac-2 Binding Protein Glycosylation isomer; SVR, sustained virological response; T1DM, type 1 diabetes mellitus.

was a 53-year-old woman. Based on retrospective history taking, she had previously been informed of HCV antibody positivity but did not receive treatment. Her ALT level at presentation was 17 U/L. She consented to DAA treatment with GLE/PIB and achieved an SVR.

4 | Discussion

This study details the planning, set-up, and successful implementation of a cohort-based micro-elimination strategy in Nagawa town to promote HCV antibody testing. A high participation rate, in particular among the elderly, revealed an age-related increase in HCV antibody positivity, and three residents were newly identified as having active HCV infection. Most HCV antibody positive individuals had a history of HCV clearance or treatment. These findings highlight the feasibility and effectiveness of a community-based approach to HCV screening and micro-elimination.

A comprehensive HCV antibody testing campaign was conducted by targeting all adult residents aged ≥ 20 years in Nagawa town, a rural area in Japan. Integrating testing into routine health check-ups, outpatient visits, and mailed invitations yielded 3121 participants, or 62.1% of the eligible population—slightly higher than the rate reported in Taiwan (58.7%) and substantially higher than that observed in a U.S. emergency-department cohort of baby boomers (20.9%) [12, 17]. Testing rates did not differ among the town's four areas, likely because every household lies within ~11 km of the sole hospital—well below the 16.1 km distance linked to reduced healthcare utilization—and because a demand-responsive transport system is available [18]. From a public-health perspective, the particularly high uptake in older adults is important. Historical exposure routes make this group a logical focus, and frequent clinic visits for chronic diseases provide convenient testing opportunities—factors that likely contributed to their higher participation. These trends are also reflected in Figure 3, which demonstrates that outpatient testing accounted for a large share of participation among the late-stage elderly, whereas health check-ups were more dominant among early-stage elderly, and mailed invitation-based consent was more effective among adults [19]. DAAs remain effective and well-tolerated in the elderly [2, 3], and Japanese guidelines recommend therapy regardless of age. Conversely, the lower uptake among younger adults signals a gap. Because they interact less with healthcare services and may not perceive themselves at risk, digital outreach—such as social-media reminders and messaging apps—could improve awareness and testing [20].

As a result, 28 residents were finally found to be HCV antibody positive (0.897%) and three were confirmed to have active viremia after HCV core antigen testing and subsequent HCV RNA confirmation, yielding an HCV carrier rate of 0.096%. This suggests that the actual prevalence of chronic HCV infection in Nagawa town is extremely low, reflecting the success of Japan's long-standing public health efforts that include early detection programs and ready access to DAA therapy. Among the 28 HCV antibody-positive individuals, 25 were classified as HCV clearance status, with over half having a confirmed treatment history. This result underscored the effectiveness of national hepatitis management policies such as the Basic Act on Hepatitis Control. The low prevalence of viremic cases was also consistent with national data showing a year-on-year decline in HCV incidence, particularly among younger generations [21]. Nevertheless, the discovery of three previously unrecognized viremic cases highlighted the importance of ongoing

surveillance. Importantly, all 3 carriers were successfully linked to clinical follow-up, and 2 achieved an SVR by DAA therapy. Consequently, 27 of the 28 HCV antibody-positive individuals were either confirmed SVR cases or had resolved infections, and survival analysis showed no significant difference in prognosis compared with antibody-negative individuals. This further supports the clinical importance of achieving SVR through DAA therapy. Although Japan has a robust hepatitis care system, individual-level barriers such as limited awareness, stigma, and low perceived need may hamper progress toward micro-elimination. Hence, even with a low carrier rate, sustained community-based screening, active case management, and ongoing education remain essential to fully eliminate HCV.

Although our findings align with the WHO's elimination targets, the Nagawa data suggest that some Japanese municipalities are already entering the final phase of HCV case finding. With only 0.096% active viremia, negligible onward transmission, and full linkage to care, a "virological elimination" benchmark—defined by the virtual absence of carriers—may be warranted. Setting such municipality-level metrics would provide a sensitive gauge of national progress toward elimination. The 62% testing coverage and 100% linkage achieved in Nagawa rested on three pillars: (i) close municipal–hospital coordination, (ii) integration of antibody testing into routine check-ups and outpatient visits, and (iii) proactive outreach that combined point-of-care opt-in with mailed opt-out invitations. These elements can be reproduced in other rural or semi-rural towns, which together make up a substantial share of Japan's population. Urban areas will require adaptations—use of multi-provider networks, digital reminders, and home-based testing kits—but the core strategies of coordination, integration, and outreach remain applicable. By tailoring the Nagawa model to local contexts, Japan can close the remaining regional gaps and accelerate progress toward nationwide HCV elimination [22, 23].

To our knowledge, this is the first community-wide, municipality-level cohort study of HCV micro-elimination in Japan, as confirmed by a PubMed search using terms including "hepatitis C," "micro-elimination," "Japan," and "community-based" (no similar studies found as of May 2025). While many internationally reported micro-elimination efforts have focused on high-risk populations such as people who inject drugs and prison population [24], few studies have described municipality-wide, population-based screening approaches in rural communities. Our study therefore provides novel insights into community-driven elimination strategies that extend beyond traditional high-risk cohorts. Future applications of this model in other municipalities may contribute to closing regional gaps and accelerating progress in view of the national goal of HCV elimination by 2030. By taking the initiative, local governments —like Nagawa town did—can serve as central coordinators, building upon routine health services and proactively seeking partnerships with industry. This approach makes implementation both financially and logistically feasible, even in the absence of external research funding.

This prospective population-based study demonstrated the feasibility of cohort-wide HCV screening in a rural Japanese town; however, several limitations should be considered. First, there may have been selection bias since individuals who participated in health check-ups or outpatient care were more likely to undergo HCV testing owing to higher health awareness as compared with non-participants. Future endeavors should include more active outreach to medically underserved populations, including workplace-based screening and mobile testing units. Second, the generalizability of our findings may be limited as Nagawa town benefits from a relatively cohesive community and centralized medical infrastructure, which may not reflect conditions in other areas. Similar initiatives in diverse settings will help broaden the applicability of our model. Third, although the study provides valuable cross-sectional data, it does not capture new or recurrent infections over time. Longitudinal follow-up will be essential to assess the long-term impact of micro-elimination strategies. Lastly, although we achieved high participation and follow-up rates, detailed clinical and behavioral data, including prior medical exposure and risk behaviors, were not systematically collected. Integrating structured interviews and electronic health records may better characterize the population at risk to guide more targeted interventions. Despite these limitations, the prospective design, high coverage rate, and strong linkage to care support the utility of this approach as a model for community-based HCV elimination.

5 | Conclusion

The Nagawa Project demonstrated the feasibility of a cohort-based HCV micro-elimination strategy in a rural setting. By combining routine health services with targeted outreach, over 60% of residents were screened, leading to the identification of 3 viremic cases, 2 of which were successfully treated. This approach shows that localized community-driven strategies can effectively identify and manage HCV infections toward regional elimination. The Nagawa Project offers a practical model for translating national HCV goals into local action to achieve the WHO's 2030 targets.

Acknowledgments

We gratefully acknowledge the valuable contributions of Yuki Akahane and Kyoko Serizawa to this study. Yuki Akahane played a central role in conducting and managing the laboratory analyses, whereas Kyoko Serizawa provided critical administrative support throughout the research process. Although both are no longer affiliated with our institution and did not participate in the preparation or final approval of the manuscript, their efforts were instrumental in the successful execution of this study. We also wish to express our sincere appreciation to Kanako Miyahara, Yoshiaki Kobayashi, and Tsuyoshi Nagai of Nagawa Town for their essential administrative support throughout the project. We would like to thank Takeji Umemura for his valuable contributions to the study design and initial discussions. Due to personal reasons, he could not participate in the manuscript preparation. We also thank Trevor Ralph as the Senior Editor of Impact Language Services for his English editorial assistance.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. K. Kiyosawa, T. Sodeyama, E. Tanaka, et al., "Interrelationship of Blood Transfusion, Non-A, Non-B Hepatitis and Hepatocellular Carcinoma: Analysis by Detection of Antibody to Hepatitis C Virus," *Hepatology* 12, no. 4 (1990): 671–675, https://doi.org/10.1002/hep.1840120409.

2. A. Sugiura, S. Joshita, T. Umemura, et al., "Past History of Hepatocellular Carcinoma Is an Independent Risk Factor of Treatment Failure in Patients With Chronic Hepatitis C Virus Infection Receiving Direct-Acting Antivirals," *Journal of Viral Hepatitis* 25, no. 12 (2018): 1462–1471, https://doi.org/10.1111/jvh.12973.

3. A. Sugiura, S. Joshita, Y. Yamashita, et al., "Effectiveness of Glecaprevir/Pibrentasvir for Hepatitis C: Real-World Experience and Clinical Features of Retreatment Cases," *Biomedicines* 8, no. 4 (2020): 74, https://doi.org/10.3390/biomedicines8040074.

4. A. Heffernan, G. S. Cooke, S. Nayagam, M. Thursz, and T. B. Hallett, "Scaling up Prevention and Treatment Towards the Elimination of Hepatitis C: A Global Mathematical Model," *Lancet* 393, no. 10178 (2019): 1319–1329, https://doi.org/10.1016/s0140-6736(18)32277-3.

5. WHO Guidelines Approved by the Guidelines Review Committee, *WHO Guidelines on Hepatitis B and C Testing* (World Health Organization, 2017).

6. D. Tordrup, Y. Hutin, K. Stenberg, et al., "Additional Resource Needs for Viral Hepatitis Elimination Through Universal Health Coverage: Projections in 67 Low-Income and Middle-Income Countries, 2016–30," *Lancet Global Health* 7, no. 9 (2019): e1180–e1188, https://doi.org/10.1016/s2214-109x(19)30272-4.

7. T. Kanto, "Messages From Japan Policy for Viral Hepatitis," *Global Health & Medicine* 3, no. 5 (2021): 249–252, https://doi.org/10.35772/ghm.2021.01078.

8. H. Razavi, Y. Sanchez Gonzalez, C. Yuen, and M. Cornberg, "Global Timing of Hepatitis C Virus Elimination in High-Income Countries," *Liver International* 40, no. 3 (2020): 522–529, https://doi.org/10.1111/liv.14324.

9. The CDA Foundation, *Hepatitis C – Japan* (CDA Foundation, 2025), https://cdafound.org/polaris/database-query/.

10. T. Akita, J. Tanaka, M. Satake, et al., "Meta-Regression Analysis of Sex- and Birth Year-Specific Prevalence of HBsAg and Anti-HCV Among Un-Diagnosed Japanese: Data From the First-Time Blood Donors, Periodical Health Checkup, and the Comprehensive Health Checkup With Lifestyle Education (Ningen Dock)," *Journal of Epidemiology* 30, no. 9 (2020): 420–425, https://doi.org/10.2188/jea.je20190055.

11. K. J. Moore, A. Gauri, and T. Koru-Sengul, "Prevalence and Sociodemographic Disparities of Hepatitis C in Baby Boomers and the US Adult Population," *Journal of Infection and Public Health* 12, no. 1 (2019): 32–36, https://doi.org/10.1016/j.jiph.2018.08.003.

12. J. K. Cornett, V. Bodiwala, V. Razuk, D. Shukla, and N. Narayanan, "Results of a Hepatitis C Virus Screening Program of the 1945–1965 Birth Cohort in a Large Emergency Department in New Jersey," *Open Forum Infectious Diseases* 5, no. 4 (2018): ofy065, https://doi.org/10.1093/ofid/ofy065.

13. B. D. Smith and A. K. Yartel, "Comparison of Hepatitis C Virus Testing Strategies: Birth Cohort Versus Elevated Alanine Aminotransferase Levels," *American Journal of Preventive Medicine* 47, no. 3 (2014): 233–241, https://doi.org/10.1016/j.amepre.2014.05.011.

14. B. D. Smith, R. L. Morgan, G. A. Beckett, Y. Falck-Ytter, D. Holtzman, and J. W. Ward, "Hepatitis C Virus Testing of Persons Born During 1945–1965: Recommendations From the Centers for Disease Control and Prevention," *Annals of Internal Medicine* 157, no. 11 (2012): 817–822, https://doi.org/10.7326/0003-4819-157-9-201211060-00529.

15. J. V. Lazarus, S. Wiktor, M. Colombo, and M. Thursz, "Micro-Elimination - A Path to Global Elimination of Hepatitis C," *Journal of Hepatology* 67, no. 4 (2017): 665–666, https://doi.org/10.1016/j.jhep.2017.06.033.

16. H. Kobayashi, S. Joshita, Y. Akahane, et al., "Protocol: Prospective Observational Study Aiming for Micro-Elimination of Hepatitis C Virus in Nagawa Town: The Nagawa Project," *PLoS One* 16, no. 8 (2021): e0256711, https://doi.org/10.1371/journal.pone.0256711.

17. T. H. Yang, Y. J. Fang, S. J. Hsu, et al., "Microelimination of Chronic Hepatitis C by Universal Screening Plus Direct-Acting Antivirals for Incarcerated Persons in Taiwan," *Open Forum Infectious Diseases* 7, no. 8 (2020): ofaa301, https://doi.org/10.1093/ofid/ofaa301.

18. G. F. Nemet and A. J. Bailey, "Distance and Health Care Utilization Among the Rural Elderly," *Social Science & Medicine* 50, no. 9 (2000): 1197–1208, https://doi.org/10.1016/s0277-9536(99)00365-2.

19. J. Tanaka, A. Kurisu, M. Ohara, et al., "Burden of Chronic Hepatitis B and C Infections in 2015 and Future Trends in Japan: A Simulation Study," *Lancet Regional Health–Western Pacific* 22 (2022): 100428, https://doi.org/10.1016/j.lanwpc.2022.100428.

20. W. C. W. Wong, G. Marley, J. Li, et al., "A Randomized Controlled Trial Enhancing Viral Hepatitis Testing in Primary Care via Digital Crowdsourced Intervention," *npj Digital Medicine* 5, no. 1 (2022): 95, https://doi.org/10.1038/s41746-022-00645-2.

21. K. Ko, T. Akita, M. Satake, and J. Tanaka, "Epidemiology of Viral Hepatitis C: Road to Elimination in Japan," *Global Health & Medicine* 3, no. 5 (2021): 262–269, https://doi.org/10.35772/ghm.2021.01069.

22. T. Okui and N. Nakashima, "Analysis of the Association Between Areal Socioeconomic Deprivation Levels and Viral Hepatitis B and C Infections in Japanese Municipalities," *BMC Public Health* 22, no. 1 (2022): 681, https://doi.org/10.1186/s12889-022-13089-w.

23. K. Okushin, T. Kanto, M. Korenaga, et al., "Real-World Trends in Acute Viral Hepatitis in Japan: A Nationwide Questionnaire-based Survey," *Hepatology Research* 55, no. 3 (2025): 301–308, https://doi.org/10.1111/hepr.14123.

24. S. Lens, A. Miralpeix, M. Gálvez, et al., "HCV Microelimination in Harm Reduction Centres Has Benefits Beyond HCV Cure but Is Hampered by High Reinfection Rates," *JHEP Reports* 4, no. 12 (2022): 100580, https://doi.org/10.1016/j.jhepr.2022.100580.