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Village-to-village screening for hepatitis B and C using quantitative HBsAg and anti-HCV testing with reflex HCV core antigen tests in the remote communities of a resource-rich setting: a population-based prospective cohort study

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ABSTRACT

Objectives Community-based screening for hepatitis B virus (HBV) and hepatitis C virus (HCV) is essential for hepatitis elimination. This study attempted to increase screening accessibility and efficacy by using alternative tools.

Design Population-based prospective cohort study.

Setting Hepatitis elimination program at Yunlin County, Taiwan.

Participants All 4552 individuals participated in 60 screening sessions of a community-based HBV and HCV screening project in five rural townships with approximately 95 000 inhabitants in central-western Taiwan.

Interventions To increase accessibility, 60 outreach screening sessions were conducted in 41 disseminative sites. Quantitative HBV surface antigen (qHBsAg) and anti-HCV testing with reflex HCV core antigen (HCV Ag) tests were employed as alternative screening tools.

Main outcome measures Calculate village-specific prevalence of HBsAg, anti-HCV and HCV Ag and establish patient allocation strategies according to levels of qHBsAg HCV Ag and alanine aminotransferase (ALT).

Results Of 4552 participants, 553, 697 and 290 were positive for HBsAg, anti-HCV and HCV Ag, respectively; 75 of them had both HBsAg and anti-HCV positivity. The average (range) number of participants in each screening session was 98 (31–150). The prevalence rates (range) of HBsAg, anti-HCV and HCV Ag were 12.1% (4.3%–19.4%), 15.3% (2.6%–52.3%) and 6.4% (0%–30.2%), respectively. The HCV Ag positivity rate among anti-HCV-positive participants was 42% (0%–100%). Using cut-off values of >200 IU/mL for qHBsAg, >3 fmol/L for HCV Ag and >40 IU/mL for ALT as criteria for patient referral, we noted an 80.2% reduction in referral burden. Three villages had high anti-HCV prevalences of 52.3%, 53.8% and 63.4% with corresponding viraemic prevalences of 23.2%, 30.1% and 22% and thus constituted newly identified HCV-hyperendemic villages.

Conclusion Outreach hepatitis screening increases accessibility for residents in rural communities. Screening HBV and HCV through qHBsAg and HCV Ag tests provides information concerning viral activities, which might be conducive to precise patient allocation in remote communities.

Strengths and limitations of this study

- ► This study is aimed to increase accessibility and efficacy of hepatitis screening by using an alternative algorithm which include reflex confirmatory testing.
- ► Hepatitis screening tools that provide additional information regarding viral activity and treatment eligibility can help guide precise patient referral.
- ► Our hepatitis screening strategy allows an increase in accessibility for residents, particularly the elderly, in remote communities.
- ► Because of the use of high flow assays used in this study, the use of this algorithm is probably not as appropriate in resource-limited settings.

INTRODUCTION

Hepatitis B virus (HBV) or hepatitis C virus (HCV) infections have long constituted a global public health problem because they are leading causes of liver-related morbidity and mortality, with complications including cirrhosis, hepatocellular carcinoma and death.[1] Approximately 30% of the world's population has serological evidence of current or past HBV infection; moreover, 123 million people are positive for anti-HCV antibodies (anti-HCV), of whom 71 million have active viraemic infections.[2 3] Because chronic carriers of hepatitis viruses are generally asymptomatic, most people infected with

HBV and/or HCV remain unaware of their infection and frequently present with advanced disease, and they may become a source of infection transmission.[4 5] Therefore, the burden of chronic HBV and HCV infections remains high, particularly in Asia and Africa, despite the well-established routes of the acquisition of these infections and effective strategies for the prevention and treatment of the infections.[6]

WHO has set ambitious goals for the elimination of HBV and HCV by 2030, this is achievable as there are highly effective, safe and well-tolerated antiviral agents and vaccines against hepatitis virus infections.[7] Precise and cost-saving tools for screening and diagnosing chronic viral hepatitis infections constitute the gateway to the prevention and treatment of HBV and HCV infections to achieve the aforementioned WHO goals.[8] Screening and early identification of asymptomatic people with chronic HBV or HCV infection can not only enable them to receive treatment to improve their health status but also prevent transmission by linking them to interventions such as risk behaviour counselling and HBV vaccination. For remote and rural communities that typically face difficulties in accessing medical resources, screening strategies to extensively identify people living with hepatitis and to efficaciously refer individuals eligible for treatment constitute a crucial component of an integrated elimination programme.[8]

HBV surface antigen (HBsAg) and HCV antibody (anti-HCV) have been the standard tools for screening HBV and HCV, respectively, and were adapted and endorsed in the recent WHO guidelines.[9] However, the traditional HBsAg and anti-HCV testing strategy involves a two-step diagnostic approach: In the first step, an anti-HCV testing is performed; in the second step, a sequential nucleic acid testing is executed in a central diagnostic laboratory to establish a diagnosis of active infection.[9] This relatively expensive and complicated two-step strategy hinders screening effectiveness, as indicated by previous studies that have reported large declines in the number of anti-HCV-positive patients who received confirmatory HCV RNA testing.[10 11] A simplified single-step HCV testing strategy was revealed to be more effective and cost-effective than the traditional two-step testing approach.[12] Technically, the feasibility and cost-effectiveness of this single-step strategy would be increased if HCV RNA testing is replaced by the cheaper HCV core antigen (HCV Ag) testing in an outreach screening setting.[13] For HBV, research revealed that linking HBsAg screening to HBV treatment is cost-effective, even at low HBsAg prevalence levels.[14] However, not all individuals positive for HBsAg or anti-HCV experience the same disease consequences; hence, prioritising only treatment-eligible individuals for referral can prevent futile and tiring journeys for those residing in remote and resource-limited regions.

The availability and rapid evolution of quantitative HBsAg (qHBsAg) and HCV core Ag (HCV Ag) assays have led to the remodelling of hepatitis screening and intervention strategies.[15 16] qHBsAg level is correlated with HBV DNA level in asymptomatic HBV carriers and can facilitate the task of differentiating immune tolerance from immune clearance in hepatitis B e antigen (HBeAg)-positive patients. Furthermore, qHBsAg level can be considered a surrogate marker of infected hepatocytes and can predict disease activity and spontaneous HBsAg seroclearance in HBeAg-negative patients.[16 17] HCV Ag has a strong positive correlation with HCV RNA and can be a useful tool for community screening.[18 19] Because not all anti-HCV-positive patients are actually viraemic and because a considerable proportion of HBV-infected individuals—especially HBeAg-negative patients with low HBsAg titers—have a benign clinical course, a strategy for identifying and precisely referring high-risk or treatment-eligible patients is crucial in remote and rural communities. Accordingly, the objective of this study was to develop a strategy for increasing the accessibility and efficacy of community-based screenings by using qHBsAg and anti-HCV with reflex HCV Ag testing in a remote and rural area of Taiwan with a high prevalence of viral hepatitis.

METHODS

Overview of study design, participants and setting

Chang Gung Memorial Hospital, Yunlin branch, is located in rural coastal central-western Taiwan with a particularly high prevalence of chronic viral hepatitis.[20] The investigated areas are among those with the oldest populations and among those with the most limited accessibility to medical resources in Taiwan. The aforementioned hospital implemented 60 outreach medical care services including hepatitis screenings from March through September 2018 at 41 sites among 5 surrounding townships, namely Dacheng, Lunbei, Baojhong, Dongshih and Sihhu, which had approximately 95 000 residents, as calculated in 2019 (figure 1). The screening campaigns were generally held in rural villages that were remote from populous downtown areas to allow the surrounding rural inhabitants to randomly walk in without any restriction. Blood specimens were collected during the rural visits for central laboratory assays, and the results were shared back to the participants via postal mail. Patients eligible for referral to further care would be notified by phone. Written informed consent was obtained from all participants.

Data measurement

The qHBsAg and HCV Ag cut-off values for patient referral were set at 200 IU/mL and 3 fmol/L, respectively.[21 22] The reason behind the cut-off value of qHBsAg was that a qHBsAg level of >200 IU/mL had the highest accuracy in predicting an HBV DNA level of >2000 IU/mL, and the corresponding negative predictive value assessed through receiver operating characteristic curve analysis was 85.9% (95% CI 76.2% to 92.7%)[21]; moreover, the aforementioned cut-off value of HCV Ag was selected because an

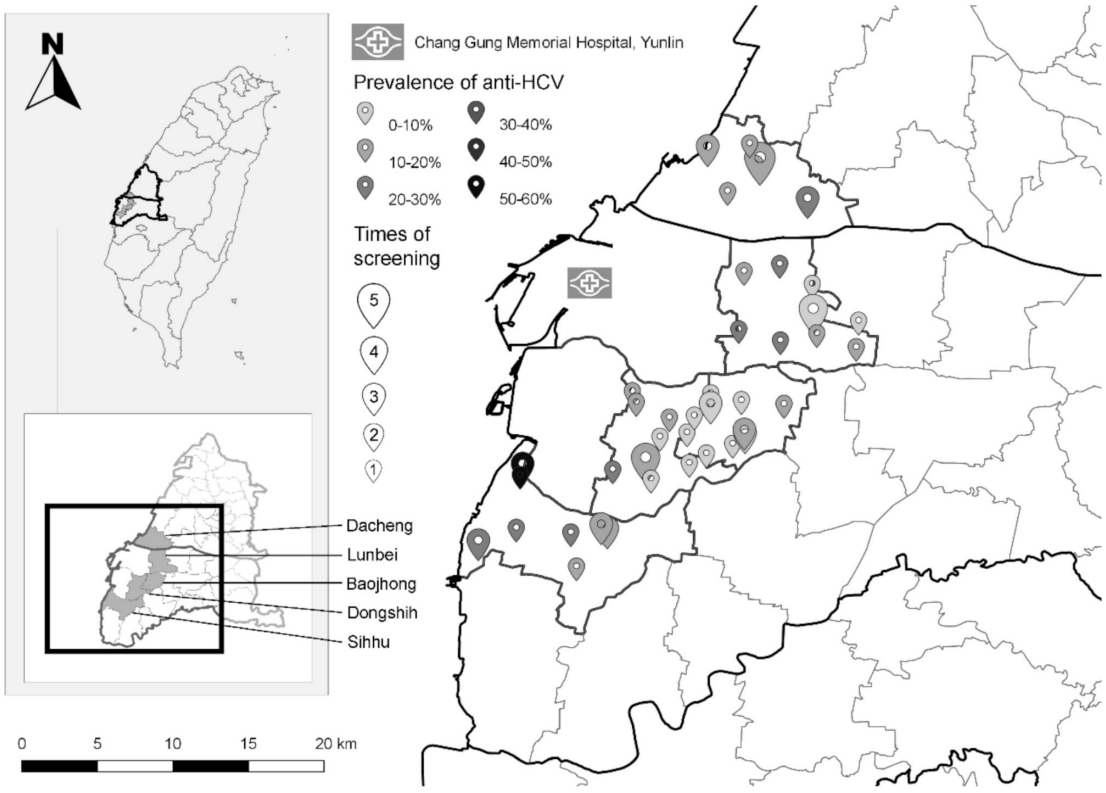

Figure 1 Distribution of the 60 outreaching screenings. HCV, hepatitisC virus.

HCV Ag level of >3 fmol/L had the highest accuracy in predicting HCV viremia, with the corresponding positive predictive value being 99%.[22]

Laboratory methods

All blood tests were done in a central laboratory. Markers used for hepatitis screening included qHBsAg, anti-HCV, HCV Ag, alanine aminotransferase (ALT) and aspartate aminotransferase. To examine the correlation between HCV Ag and anti-HCV, tests for both anti-HCV and HCV Ag were performed for the first 1000 participants. Among the first 1000 participants, all individuals who were positive for HCV Ag were positive for anti-HCV; therefore, HCV Ag was tested only for anti-HCV-positive individuals among the subsequent 3552 participants. HBV DNA was assessed for all participants who were positive for HBsAg (qHBsAg ≥0.5 IU/mL). In addition, HCV RNA was assessed for the first 1000 participants who were positive for anti-HCV and the subsequent 3552 participants who were positive for HCV Ag.

Anti-HCV was detected on the Cobas e411 analyzer through an automated electro chemiluminescence immunoassay executed using the Elecsys Anti-HCV II assay kit (Roche Diagnostics GmbH, Mannheim, Germany). The Architect HBsAg assay (Abbott Laboratories, Sligo, Ireland) was used for qHBsAg detection. This assay is an automated chemiluminescent microparticle immunoassay (CMIA) for determining qHBsAg in human serum and plasma and has a sensitivity of ≤0.5 IU/mL. The Architect HCV Ag assay (Abbott Laboratories) was used to detect HCV Ag. This assay is a two-step CMIA technology-based immunoassay for the quantitative measurement of HCV Ag. Specimens with levels of ≥3 fmol/L were considered to be reactive for HCV Ag, whereas those with levels of <3 fmol/L were considered to be non-reactive. HBV DNA was detected using the Cobas AmpliPrep/Cobas TaqMan HBV test V.2.0 (Roche Molecular Systems, South Branchburg, NJ, USA). An HBV DNA level of 16.4 IU/mL could be detected with a hit rate of >95%. HCV RNA was detected using the Cobas AmpliPrep/Cobas TaqMan HCV quantitative test V.2.0 (Roche Molecular Systems). This assay demonstrated a limit of detection and lower limit of quantification of 15 IU/mL across all HCV genotypes.

Statistical analysis

Sample characteristics

Patient age is expressed as mean±SD. Other continuous values are expressed as percentages or ranges as indicated.

All statistical analyses were performed using SAS software (V.9.4, SAS Institute).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of the research.

RESULTS

Village-specific prevalence of HBsAg, anti-HCV and HCV Ag

A total of 4552 individuals participated in the 60 screening sessions. Of the 4552 participants, 553, 697 and 290 were positive for HBsAg, anti-HCV and HCV Ag, respectively;

Table 1 Village-specific prevalence of HBsAg, anti-HCV and HCV Ag

Township	Session	N	HBsAg(+)	Anti-HCV(+)	HCV Ag(+)	HCV Ag/anti-HCV
Dacheng	12	35–147	3.4%–13.3%	8.1%–30.5%	0–17.9%	0%–67%
	Subtotal	969	90 (9.3%)	163 (16.8%)	73 (7.5%)	45%
Lunbei	12	55–145	2.2%–16.4%	3.1%–24.4%	0%–12.1%	0%–64%
	Subtotal	1102	116 (10.5%)	140 (12.7%)	58 (5.3%)	41%
Baojhong	12	28–123	4.4%–18.4%	0%–17.9%	0%–5.3%	0%–50%
	Subtotal	627	75 (12%)	49 (7.8%)	12 (1.9%)	24%
Dongshih	12	34–141	10.4%–28.6%	2.9%–20.8%	0%–12.5%	0%–100%
	Subtotal	1052	166 (15.8%)	122 (11.6%)	46 (4.4%)	38%
Sihhu	12	33–113	5.6%–17.7%	10.7%–63.4%	1.8%–30.1%	17%–60%
	Subtotal	802	106 (13.2%)	223 (27.8%)	101 (12.6%)	45%
	Total	4552	553 (12.1%)	697 (15.3%)	290 (6.4%)	42%

%: Number of test(+)/subtotal.
HBsAg, Hepatitis B virus surface antigen; HCV, hepatitis C virus; HCV Ag, HCV core antigen .

75 were positive for both HBsAg and anti-HCV. Table 1 presents the village-specific prevalence of HBsAg, anti-HCV and HCV Ag. Detailed figures for each of the 60 screening sessions are provided in online supplemental table 1. The average (range) number of participants in each screening session was 98 (31–150). The prevalence rates (range) of HBsAg, anti-HCV and HCV Ag were 12.1% (4.3%–19.4%), 15.3% (2.6%–52.3%) and 6.4% (0%–30.2%), respectively. The positive rate (range) of HCV Ag among anti-HCV-positive participants was 46% (0%–100%). Three villages had a high anti-HCV prevalence of >50% in screening sessions 4 (52.3%), 9 (53.8%) and 37 (63.4%) with corresponding viraemic prevalences of 23.2%, 30.1% and 22%, respectively. Therefore, these three were considered to constitute newly identified HCV-hyperendemic villages.

Patient allocation strategies according to grouping by qHBsAg and anti-HCV

The participants were divided into four groups according to positivity for HBsAg (B^+) and anti-HCV (C^+): the first group comprised those who were dual positive for HBsAg and anti-HCV (B^+C^+), second group comprised those who were positive for HBsAg but not positive for anti-HCV (B^+C^-), third group comprised those who were positive for anti-HCV but not positive for HBsAg (B^-C^+) and fourth group comprised those who were dual negative for HBsAg and anti-HCV (B^-C^-). To avoid ineffective referral processes and achieve precise referral, patients expected to be at a high risk of liver disease morbidities or candidates eligible for antiviral therapy were prioritised for hospital referral. Table 2 presents a summary of the referral strategy and the corresponding reduction in referral burden. In the B^+C^+ group, prioritising only participants with qHBsAg levels of >200 IU/mL or HCV Ag levels of >3 fmol/L for referral reduced the referral burden by 40% (30 out of 75 people). Moreover, in the B^+C^- group, prioritising those with qHBsAg levels of >200 IU/mL or ALT levels of >40 IU/L for referral reduced the referral burden by 52.6% (251 out of 478 people). In the B^-C^+ group, prioritising those with HCV Ag levels of >3 fmol/L or ALT levels of >40 IU/L for referral reduced the referral burden by 52% (322 out of 622 people). Finally, in the B^-C^- group, prioritising those with ALT levels of >40 IU/L resulted in a 90.5% reduction (3049 out of 3377 people) in the referral burden. The established referral strategy achieved a total referral burden reduction of 80.2% (3652 out of 4552 people). Reduction in the referral rate was calculated as : [1−(the number of patients eligible for referral by qHBsAg and HCV Ag)/(the number of patients eligible for referral by traditional HBsAg and anti-HCV)]×100%.

DISCUSSION

The worldwide annual mortality rate for liver diseases attributed to HBV and HCV is approximately 1.5 million, which is comparable to or even higher than the rates observed for other infectious diseases such as HIV and tuberculosis.[23] Delaying treatment for HBV and HCV not only increases the risk of liver morbidity and mortality but also creates a reservoir for disease transmission. The availability of short and easily tolerable treatment courses involving direct-acting antiviral drugs has made HCV elimination feasible. Although no comparable cure exists for HBV, nucleos(t)ide analogues with a high barrier to resistance, such as entecavir and tenofovir, can effectively suppress HBV and are cost-effective.[24] In addition, vaccination against HBV has proven extremely effective.[25] However, an extensive gap exists between the numbers of hepatitis patients infected and those diagnosed.[4 5] This is particularly true for populations with limited medical resources or in settings with inadequate access to medical resources. Among people infected with viral hepatitis, those with access to healthcare systems

Table 2 Grouping by qHBsAg(B^+) and anti-HCV(C^+)

Group	N (%)	Subgroup	n (%)*
B^+C^+	75 (1.6%)	qHBsAg≥200 and HCV Ag>3	7
67.8±10.3 years		qHBsAg≥200 and HCV Ag≤3	22
Male: 40%		qHBsAg<200 and HCV Ag>3	16
		qHBsAg<200 and HCV Ag≤3	30 (40%)
B^+C^-	478 (10.5%)	qHBsAg≥200 and ALT>40	36
61.2±12.6 years		qHBsAg≥200 and ALT≤40	173
Male: 38.9%		qHBsAg<200 and ALT>40	17
		qHBsAg<200 and ALT≤40	251 (52.6%)
		Incomplete data	1
B^-C^+	622 (13.7%)	HCV Ag>3 and ALT>40	92
70.6±10.3 years		HCV Ag>3 and ALT≤40	175
Male: 32%		HCV Ag≤3 and ALT>40	30
		HCV Ag≤3 and ALT≤40	322 (52%)
		Incomplete data	3
B^-C^-	3377 (74.2%)	ALT≤40	3049 (90.5%)
63.1±15.5 years		40<ALT≤80	274
Male: 37.9%		ALT>80	47
		Incomplete data	7
Total	4552 (100%)	**Non-referral/total**	3652/4552 (80.2%)

N=4552, 64±14.8 years, male: 37.2%.
Unit: IU/mL for qHBsAg, fmol/L for HCV Ag and IU/L for ALT.
*Rate of reduction on referral burden by % : [1−(the number of patients eligible for referral by qHBsAg and HCV Ag)/(the number of patients eligible for referral by traditional HBsAg and anti-HCV)]×100%.
ALT, alanine aminotransferase; HCV, hepatitis C virus ; HCV Ag, HCV core antigen; qHBsAg, quantitative HBV surface antigen.

would be controlled or even treated; hence, identifying unaware patients and linking them to care constitute a major obstacle to successful hepatitis elimination programmes.[8 26] We propose an outreach HBV and HCV screening project using alternative assays to identify infected individuals in resource-limited rural and hard-to-reach communities and enhance their accessibility to healthcare resources.

Understanding the burden of viral hepatitis is essential for stakeholders embarking on hepatitis treatment programmes. Data regarding hepatitis prevalence are limited because of the inherent difficulties of population screening and the cost of testing.[26] According to a WHO report, only 9% of approximately 257 million people with chronic HBV infection and 20% of 71 million with chronic HCV infection were estimated to have been diagnosed.[23] The increasing availability of drugs has enabled rapid scale up of testing and treatment of patients; hence, attention has shifted to the challenge of identifying undiagnosed individuals, especially those in resource-limited and difficult-to-reach communities. Accordingly, new virological tools such as point-of-care tests and dried blood spots are increasingly being adopted or developed for viral hepatitis screening, diagnosis and monitoring.[27] Although these tools are advantageous for low-income and difficult-to-reach communities, they still use qualitative or quantitative evaluations of HBsAg and anti-HCV. Although HBsAg and anti-HCV were adapted in the recent WHO guidelines as the standard tools for screening HBV and HCV[9]; their applicability in the assessment of treatment eligibility is limited.[27] Our study indicated that village-to-village outreach screening can help increase the accessibility of residents and reveal hepatitis-endemic areas in remote communities. Blood specimens were collected during each screening campaign for central laboratory assays, and the results were shared back to the participants via postal mail. Patients eligible for referral was notified by phone. Use of qHBsAg and anti-HCV screening with reflex confirmatory HCV Ag tests could help identify patients with viral activity and those eligible for or requiring treatment. This efficacious strategy facilitates a 'one stop testing' and allows for precise referral while mitigating unnecessary patient transportation and is expected to reduce the number of patients lost to follow-up. Moreover, our results reveal a high proportion of anti-HCV-positive individuals and HBsAg-positive individuals who were actually not viremic or did not require treatment; these findings suggest that prevalence-screening approaches that focus on individuals with detectable HBsAg or anti-HCV should be

complemented with or substituted with approaches that focus only on individuals with active HBV or HCV infection. Conventionally, active HBV and HCV infections are identified through the detection of HBV DNA and HCV RNA, respectively. Replacing HCV RNA by HCV Ag is feasible and has been shown to be cost-effective in community-based HCV screening in Taiwan.[28]

A study investigating the acceptability and feasibility of a screen-and-treat programme using point-of-care HBsAg screening in The Gambia revealed that knowledge about HBV infection was extremely low in local communities.[29] This programme linked up to 81.3% of HBsAg-positive individuals to care, constituting a high linkage rate. However, the referral of up to 95% of these individuals was unnecessary because only 4.4% of the HBsAg-positive individuals were eligible for antiviral therapy.[29] The mentioned study adequately exemplifies the importance of community-based screening for disease awareness and precise referral of the low proportion of HBV carriers eligible for therapy. Therefore, researchers in the mentioned study developed a simple 'TREAT-B' scoring system using serum ALT and HBeAg to facilitate the identification of individuals eligible for treatment in resource-limited African countries.[30] This scoring system is inexpensive and demonstrated comparable performance to the REACH-B and WHO criteria.[31 32] Other non-invasive tools, including transient elastography, the aspartate transaminase-to-platelet ratio index, fibrosis-4 and the recently described gamma-glutamyl transpeptidase-to-platelet ratio, are all valuable in predicting the severity of liver fibrosis in patients with chronic HBV or HCV infections in various settings.[33] Another UK model incorporating bloodborne viruses including HIV, HBV and HCV combined testing into the routine blood tests in emergency departments helped identify a high number of newly diagnosed viral hepatitis case.[34] Compared with these tools, our strategy involving the use of qHBsAg and HCV Ag estimates only viral activity but not fibrosis severity. Nevertheless, our strategy exhibits superior convenience as a screening tool because it executes screening and risk identification for both HBV and HCV simultaneously.

Because the sensitivity of HCV Ag is high, the use of anti-HCV may be abandoned or supplemented by HCV Ag in the screening programme. We determined a qHBsAg level of 200 IU/mL to be the best cut-off for predicting an HBV DNA level of >2000 IU/mL. Therefore, we proposed a schematic flowchart for community hepatitis screening and patient referral in hard-to-reach communities, as illustrated in figure 2.

Our study has some limitations. First, the screening coverage was not comprehensive because we did not adopt a systematic screening approach and recruited volunteered participants. We are currently executing data linkage with the Household Registration Office of the government in order to identify screening-naïve individuals and avoid repeated screening. Second, the cut-off values for patient allocation, namely 200 IU/mL for qHBsAg and 40 IU/L for ALT, were based on the results of our cohort, which are likely to vary according to the scenarios of individual regions. A more feasible approach for our study would have been to apply ultrasonography to exclude cirrhosis before executing patient allocation. Finally, the qHBsAg and HCV Ag assays still required the use of a large, high-throughput, laboratory-based, multi-analyte analyzer. This is not necessarily a problem for screening communities within 10 km from the laboratory.

In conclusion, our study revealed that outreach screening can increase resource accessibility for residents in remote communities. It can also increase the chance

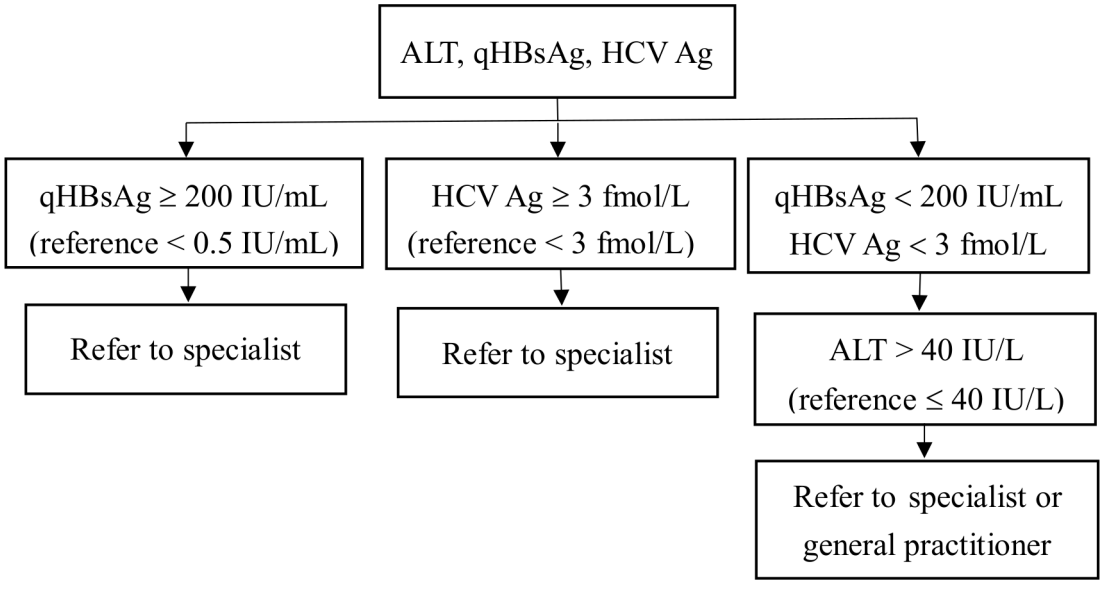

Figure 2 Proposed schematic flowchart of hepatitis screening and precise patient referral for the hard-to-reach communities. ALT, alanine aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HCV Ag, HCV core antigen; qHBsAg, quantitative HBV surface antigen.

of detecting small hepatitis-endemic villages. Screening HBV and HCV by using qHBsAg and HCV Ag tests can provide adequate information concerning viral activity. Prioritised referral of treatment-eligible individuals to hospitals can reduce the referral burden in remote areas.

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Contributors The roles of the contributors were as follows: Conceptualisation: S-NL and M-YC. Writing the manuscript: TSC and S-NL. Data curation: KCC, WMC, WNC, YCL, JHH, T-JH and WCH. Methodology and software: NTH and CYL. All authors provided critical revisions. All authors read and approved the submitted manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (IRB No. 201702196B0) and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Data are available on reasonable request. The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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