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RESEARCH ARTICLE

Efficiency of the Relink C strategy: identification and retrieval of chronic HCV patients full and partial diagnosed but unlinked to care

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ABSTRACT

Background: The existence of patients with Hepatitis C virus who were diagnosed but unlinked to care (DBUC) hinders the Hepatitis C elimination. The objectives were to present the results of the ReLink-C strategy in three Spanish hospitals and analyse its efficiency for both patients with positive viral load testing (full diagnosis) and with HCV antibodies, but without positive viral load testing (partial diagnosis); and partial diagnosis only.

Methods: The strategy was divided in two phases: Phase I, DBUC patients with complete or partial diagnosis without follow-up from Microbiology unit were searched and identified; and Phase II, missing patients were contacted by telephone and referred to Hepatology for further treatment. In addition, the characteristics (age, gender, country of origin and fibrosis status) of the lost and treated patients were collected.

Results: The three hospitals identified 3,444 patients to search for retrieval, 1,538 (45%) with full diagnosis and 1,906 (55%) partial diagnosis. Overall, about 35% (1,221/3,444) were DBUC and the ReLink-C strategy successfully localised 903 patients, of which 493 patients were linkage to care and 273 were treated. The ReLink-C strategy (full and partial diagnosis) compared to no intervention showed a reduction in liver and mortality complications (range 22-29%) with an incremental cost-utility ratio of €8,958/patient, and in case of partial diagnosis of €9,396/patient.

Conclusions: The Relink-C active search strategy enabled the retrieval and treatment of a significant number of diagnosed hepatitis C cases that would not have been detected in clinical practice. It was cost-effective for both (full and partial diagnosis) and partial diagnosis only, being in line with the 2030 hepatitis C elimination targets.

Keywords: diagnosed but unlinked to care, cost-effectiveness, HCV infection

Introduction

Hepatitis C virus (HCV) infection causes acute or chronic hepatitis, with severe clinical manifestations in chronic cases that can have potentially life-threatening consequences.[1] The World Health Organization (WHO) estimated 290,000 deaths due to HCV in 2019 from complications such as cirrhosis and hepatocellular carcinoma, out of an estimated 58 million people with chronic HCV worldwide.[1] The high effectiveness of direct-acting antivirals (DAAs), which have simplified treatment and delayed the onset of serious complications of the disease, led to the WHO's objective of eliminating liver viruses by 2030. Since the launched of the Spanish National Plan against Hepatitis C in 2015, numerous measures aimed at prevention, detection, diagnosis, and access to treatment have been promoted to reduce the morbidity and mortality caused by HCV, with 165,700 HCV patients being treated by 2023.[2–5] As diagnostics was the main challenge to achieving hepatitis C elimination by 2030, one-step diagnosis (OSTD) of active HCV infection using the same patient serum sample was implemented.[1,2,4,6] Compared to the standard diagnostic approach, OSTD reduces referral and treatment initiation times helping linkage to treatment care.[7]

Nonetheless, the existence of patients with HCV who were diagnosed but unlinked to care (DBUC) for various reasons in the health system is still a barrier to WHO's HCV elimination strategy.[4,8–14] According to the 2017-2018 Spanish survey, approximately 17% of the total individuals with diagnosed active HCV infection were unlinked to care in the National Heaths System (NHS).[15] This loss can lead to delayed diagnosis and treatment of infection, increasing the risk of serious liver complications (hepatic decompensation, hepatocellular carcinoma or the need for liver transplantation) and other comorbidities.[16] In order to work towards the elimination of HCV infection, the ReLink-C strategy was designed to identify DBUC patients link to the NHS for treatment. The strategy aims to search two types of patients (i) patients with HCV-RNA positive (HCV-RNA+) testing (full diagnosis) and (ii) patients with anti-HCV antibodies (anti-HCV+) but without evidence of positive HCV-RNA testing (partial diagnosis).

Moreover, in order to ensure the NHS sustainability, economic evaluation of these healthcare interventions is considered relevant to assess their efficiency.[17] The DAAs therapies have proven to be efficient for the treatment of chronic HCV in Spain.[18] The ReLink-C strategy has been shown to be efficient in DBUC patients with chronic HCV (HCV-RNA+)[14], but no evidence was available for the strategy applied to DBUC patients with only anti-HCV+ test. The primary objective of this study was to present the results of the ReLink-C strategy in three Spanish NHS hospitals and analyse its efficiency by pooling both types of DBUC patients: full and partial diagnosis. The secondary objective was to evaluate the efficiency in DBUC patients with partial diagnosis.

Methods

POPULATION STUDY AND CENTRES

This analysis was based on data from three Spanish hospitals: (i) the Regional University Hospital of Malaga (RUHM), with a reference population of 630,000 inhabitants; (ii) the University and Polytechnic Hospital La Fe (UHLF) of Valencia, with a reference population of 290,000 inhabitants; and (iii) the University Hospital Doctor Negrin (UHDN) of Gran Canaria, with a reference population of 350,000 inhabitants. In an informative but not restrictive manner, the protocol for the ReLink-C strategy was submitted to and approved by the respective Ethics Committee. In accordance with Spanish legislation, all data were processed confidentially in an anonymous database accessible only to the researchers.

IDENTIFICATION AND INTERVENTION

The methodology of the ReLink-C strategy consisted of two successive phases (*Supplementary:* Figure S1). The first, a retrospective search for patients eligible for treatment based on a review of medical and laboratory records (Phase I: Identification) and the second, the retrieval of these patients to re-evaluate and start treatment when necessary (Phase II: Intervention).

In the Phase I, DBUC patients were identified in the Microbiology laboratory database of each hospital, with or without the help of the hospital's IT services. The DBUC patients were divided into 'full diagnosis', defined as anti-HCV+ with HCV-RNA+, and 'partial diagnosis', defined as anti-HCV+ without evidence of subsequent HCV-RNA testing. Based on a review of medical records and the laboratory database, an attempt was made to locate all patients identified as potential DBUC patients. Clinical records were used to determine whether patients had been transferred to another healthcare area or had died. The remainder could be on treatment at the time of the search, untreated (due to comorbidity, short life expectancy) or cured. Thus, patients transferred to another healthcare setting, under treatment, untreated, cured or had died were not included. The retrospective data collected cover the period from January 2015 to December 2020 for RUHM, and from January 2010 to December 2020 for UHLF and UHDN. In addition, the patient search also differentiated the implementation of one-step diagnostics introduced in December 2018 (at RUHM), March 2018 (at UHLF), and May 2014 (at UHDN).

The phase II, an attempt was made to locate DBUC patients to offer them an appointment with a specialist for assessment and offer treatment when necessary. This was done through telephone calls (range 1-10 per patient), e-mails and/or letters. Contacted cases were categorised into those who accepted the follow-up and those who did not (due to death, refused follow-up, treatment, or appointment). All patients who attended the consultation underwent a series of tests (which included among others, analytical, genotyping, ultrasound, and elastography or FIB-4 score to stage liver fibrosis) to assess their disease condition and offer them treatment if necessary. Patients with partial diagnosis underwent HCV PCR testing to determine whether they had chronic HCV infection and, in the case of a negative HCV-RNA result, they were informed and discharged. The reasons for not starting treatment were failure attended the appointment, refusal of treatment, or comorbidity.

ECONOMIC EVALUATION

To estimate the efficiency of the ReLink-C strategy compared to no intervention, a cost-utility analysis (CUA)

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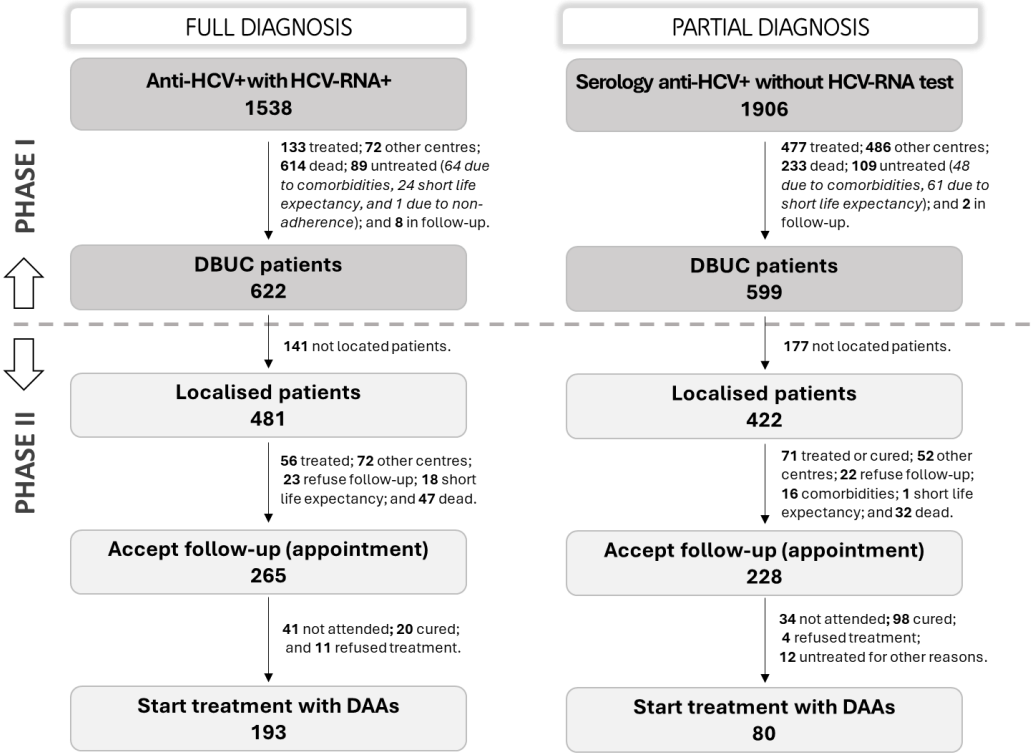
was performed for both primary and secondary objectives. The analysis used a previously validated Markov model[18] simulating the evolution of the disease through different health states over the life of the patient.

The patients included in the simulation were DBUC patients, excluding those who had been treated or cured and died (once located or accepted for follow-up). The mean age of the patients and the distribution of fibrosis states were derived from hospital-based data. The sustained virologic response (98%)[19] was used as a representative value for efficacy in treated patients. Transition probabilities, utility values, and costs of each health state were the same as those reported in the model.[18]

From the perspective of the Spanish NHS, the cost of the ReLink-C strategy included the consumption of direct healthcare resources to HCV diagnosis (*Supplementary:* Table S1, Table S4 and Table S7) and dedicated hours to search and location DBUC patients (*Supplementary:* Table S2, Table S5 and Table S8). Unit resource costs were obtained from official regional publications and published literature (Table S10)[20–24].The treatment cost was €17,126 according to a Spanish study that provided the average pharmacological cost of antiviral treatment per patient.[24] Costs were expressed in euros for the year 2024 (€, 2024).

A lifetime time horizon was applied to estimate the number and cost of liver complications, life years (LYs) gained, quality-adjusted life years (QALYs) gained, total cost of intervention (ReLink-C strategy) and total cost of non-intervention. Liver complications included decompensated cirrhosis, hepatocellular carcinoma, liver transplantation and mortality due liver disease. A discount rate of 3.0% was applied for both costs and health outcomes. Sensitivity analysis (SA) was performed varying the cost of treatment (30% and 60% less than the baseline value) to provide different approaches in the healthcare setting and cost of diagnosis (±20%).

Figure 1. Flowchart of ReLink-C strategy in patients of three hospitals in Spain.



Abbreviations: Anti-HCV+, serology positive to HCV; DAA, direct-active antiviral; DBUC, diagnosed but unlinked to care; HCV, hepatitis C virus; HCV-RNA, HCV viral load; HCV-RNA+, HCV-positive viral load.

Results

IDENTIFICATION AND INTERVENTION

The three hospitals identified a total of 3,444 patients for search and retrieval, 1,538 (45%) with *full diagnosis* and 1,906 (55%) with *partial diagnosis*.

Of the patients identified as *full diagnosis*, 622 (40%) were DBUC and selected for recovery in phase II, 133 (9%) were not selected for recovery because they had already been treated, 614 (40%) had died, 72 (5%) were from other centres, 89 (6%) were untreated due to comorbidities or short life expectancy, and 8 (1%) were in follow-up. Out of 622 DBUC patients selected for recovery in phase II, 141 (23%) were not localised. Of the successful contacts (n=481), 265 (55%) accept the hospital appointment and 193 started DAA treatment (73% of those who accepted the appointment). The reasons for non-appointment patients (n=216) were as follows: 128 (27%) were treated or were followed-up in other centres, 23 (5%) declined follow-up, 18 (4%) had comorbidities or short life expectancy, and 47 (10%) died.

Of those patients identified as *partial diagnosis,* of identified patients, 599 (22%) were DBUC and selected for recovery in phase II excluding 477 (25%) already had treated, 233 (12%) had died, 486 (25%) were from other healthcare areas, 109 (6%) were untreated due to comorbidities or short life expectance, and 2 (0,1%) were in follow-up. Out of 599 DBUC patients selected for

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recovery, 422 (70%) were contacted, of these 228 (54% of contacted) accepted the hospital appointment and finally 80 patients started DAA treatment (representing a 35% of those who accepted the appointment). The patients who were not appointed (n=194) for further treatment were due various reasons: 71 (17%) were treated or cured, 52 (11%) were followed-up in other centres, 22 (5%) refused the follow-up, 17 (4%) had comorbidities or short life expectancy, and 32 (7%) died. The Figure 1 provides a detailed flowchart of the results (based on Figure S2, Figure S3 and Figure S4, supplementary).

In overall, about 35% (1,221/3,444) of hepatitis C patients identified were DBUC and the ReLink-C strategy successfully localised 903 patients of the total of DBUC (1,221 patients with *full* and *partial diagnosis*), of which 493 patients were linkage to care and 273 were treated.

The clinical characteristics of the DBUC patients were obtained from the patients attending the appointment (*Supplementary:* Table S3, Table S6 and Table S9). The average age of the patients was 54 years, with a male majority (up to 79%). Clinical data showed that a major proportion of patients were in early stage (F0-F1) of fibrosis, either in cases of *full diagnosis* (range between 46% and 74%) as well as in cases of *partial diagnosis* (range between 42% and 76%).

There were numerical but not remarkable differences in the proportion of patients lost to follow-up before and after the introduction of one-step diagnostics.

ECONOMIC EVALUATION

For the primary objective of the ReLink-C strategy, the simulation included a pooled of 897 DBUC patients with *full diagnosis* and *partial diagnosis* (out of 1,221 candidates to contact excluding 245 treated or cured, and 79 deaths). Of the pooled DBUC patients, 273 were treated with DAAs. Total cost of the intervention (Relink-C strategy) was €234,919 corresponding to patient identification, recovery, and diagnostic. The ReLink-C strategy (including *full* and *partial diagnosis* patients) compared to no intervention showed a reduction in 22 cases of liver-related mortality and a reduction in the number of liver complications (22 cases of decompensated cirrhosis, 17 cases of hepatocellular carcinoma, and 2 liver transplantation). The total savings generated related to liver complications were €1,042,551 (Figure 2a). The CEA showed an increase of 0.35 QALYs compared to no intervention with a total incremental cost of €3,116, resulting an incremental cost-utility ratio (ICUR) of €8,958 per patient (Table 1).

In the simulation of the secondary objective, we included 398 DBUC patients with *partial diagnosis* of which 80 patients were treated. The total cost associated of the ReLink-C strategy for these type patients was €108,883. ReLink-C strategy versus no intervention also decreased a 21% liver-related mortality and between 18-25% liver complications generating total savings of €305,510 (Figure 2b). The ReLink-C strategy for *partial diagnosis* patients showed an increase of 0.23 QALYs compared to no intervention with an incremental cost of €2,158, resulting a ICUR of €9,396 per patient (Table 1).

In summary, the model results showed that the ReLink-C intervention was a cost-effective strategy in the search DBUC patients with *full* and *partial diagnosis* and with only *partial diagnosis* patients.

At full diagnosis, a 30% decrease in treatment cost decreased the ICUR to €4,462 per patient and 60% made the Relink-C strategy dominant. Variations in the cost of diagnosis varied the ICUR between €8,807 and €9,108. In partial diagnosis, SA showed a variation in the ICUR when changing the cost of treatment or the cost of diagnosis of between €450-€4,900 and €9,158-€9,634, respectively.

Discussion

Since the elimination of hepatitis requires comprehensive interventions in different public health areas, including prevention, diagnosis, and treatment, it is important to increase awareness of the contribution made by the ReLink-C strategy.

The collection data obtained provided evidence on the number of diagnosed but untreated patients and demonstrated the importance of searching and contacting these patients in contributing to achieving the HCV elimination targets set by the WHO. Furthermore, the economic evaluation determined the efficiency of this strategy to assist in decision-marking in health systems.

The results of the ReLink-C strategy in these hospitals reflect that a significant percentage (about 35%; 1221/3444) of hepatitis C patients were already diagnosed and would remain unidentified if such strategies were not implemented. This is in line with other studies on missing case finding and patient recovery in Spain and other countries.[8–14,25–29] Although it is difficult to compare the results between them due to the diversity in methodology, we can point out that they reaffirm the need to incorporate this strategy in all hospitals given its effectiveness in the recovering lost patients and in achieving their linkage to the health system.

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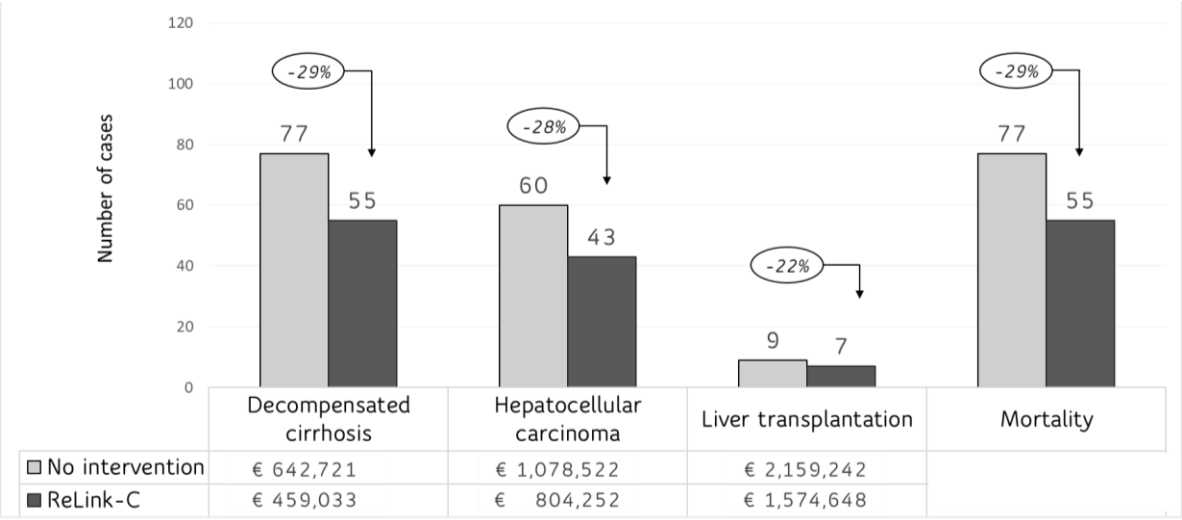
Figure 2. Number of cases and their associated costs in the lifetime of DBUC patients with (a) full and partial diagnosis (b) Only partial diagnosis

(a)



(b)

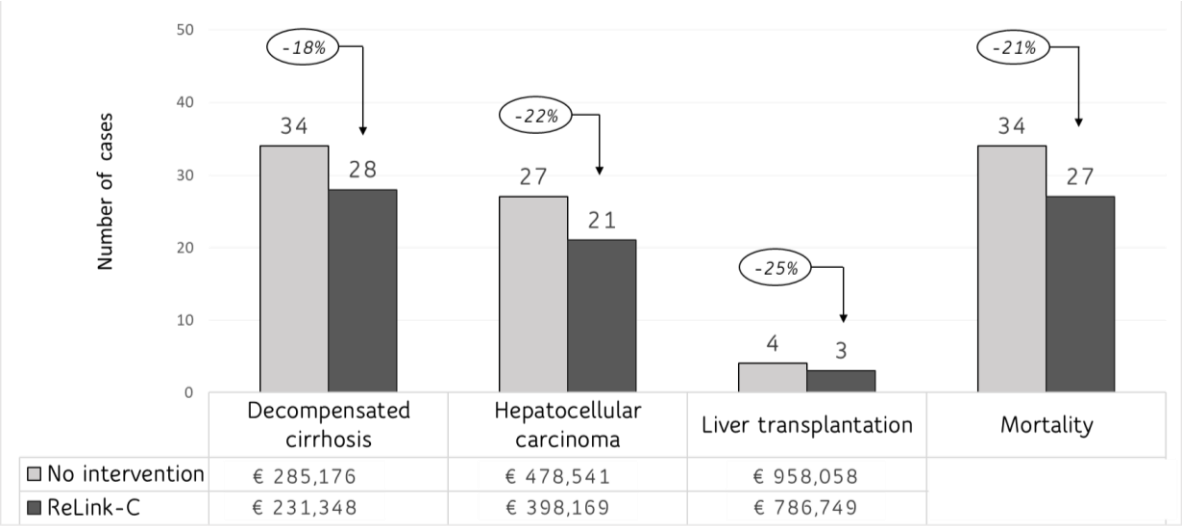


Table 1 CEA ReLink-C results per DBUC patient with full and partial diagnosis or only partial diagnosis

Type of DBUC patient	Intervention	No intervention	Difference
Full and partial diagnosis			
Health outcomes			
QALYs	10.33	9.98	0.35
Economics results			
Search, localization, and diagnosis cost	€ 262	€ 0	€ 262
Pharmacological costs	€ 5,212	€ 0	€ 5,212
Disease management cost	€ 6,546	€ 8,904	-€ 2,358
Total cost	€ 12,020	€ 8,904	€ 3,116
ICUR			**€ 8,958**
Partial diagnosis			
Health outcomes			
QALYs	10.21	9.98	0.23
Economics results			
Search, localization, and diagnosis cost	€ 274	€ 0	€ 274
Pharmacological costs	€ 3,442	€ 0	€ 3,442
Disease management cost	€ 7,346	€ 8,904	-€ 1,558
Total cost	€ 11,062	€ 8,904	€ 2,158
ICUR			**€ 9,396**

Abbreviations: CEA, cost-effectiveness analysis; DBUC, diagnosed but unlinked to care; ICUR, incremental cost-utility ratio; QALY, quality-adjusted life year.

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On the other hand, as the ReLink-C strategy was implemented differently in each hospital, one limitation of the study is related to the way in which the data provided by the microbiology service was filtered before listing patients with a complete or partial diagnosis and which affects the number of patients excluded in calculating the total number of DBUC patients of each hospital. This is reflected, for example, in the 477 patients treated within the group of those lost with incomplete diagnosis. In the case of the hospital in Malaga was assisted by the IT services for cross-referencing and data extraction, which prevented duplicate patients over the years (each patient was analysed only once considering the most recent viral load; in the case of a negative viral load by regardless of spontaneous or treatment-related clearance, it was considered as a non-missing patient). This is important because it affects the way patient flow is interpreted, as it has been different in each centre. Access to retrospective information is another limitation, as it depends on the digitalisation of medical records and the IT systems of each hospital. Furthermore, database management tends to be more complicated in reference hospitals where many of the patients attending are referred from centres in other health areas or Autonomous Regions to treat other pathologies which require a hepatitis C test. In order to be able to reach these patients, it would be necessary to establish shared databases between hospitals which would make it possible to communicate the status of their infection.

It should also be noted that the recovery rate of lost patients can vary depending on many variables and this affects the cost-effectiveness results. These include the range of years included in chart review, the involvement in the number of patients contacts attempts, whether other elimination strategies have been previously conducted in the area, and the date the one-step diagnosis was implemented.

There are several factors that have helped to achieve this strategy. Due to the need to preserve patient data without their consent, this type of strategy could not be developed if the legal framework did not facilitate it. Given the commitment to HCV elimination, the identification of HCV patients by the Public Health authorities of the Autonomous Regions or the Health Services became essential, facilitating access to clinical records and enabling professionals to contact these patients to facilitate their linkage and treatment.[30] But there is also the multidisciplinary work and the commitment to made up of microbiologists or laboratories, hepatologists, primary care or other specialities, hospital managers, statisticians, among others, involved in order to carry out this strategy. Also, the effort to recover patients beyond 5 years of retrospective search should be noted. And of course, the availability and acceptance of patients to the strategy, with a refusal rate of around 5%. The ReLink-C strategy should be the starting point for hepatitis C elimination. The success of this strategy is demonstrated by the number of patients recovered and treated, and in the cost-effectiveness results which confirm the need to give greater visibility to the results of this type of interventions by including them in global and regional elimination plans as a priority strategy towards hepatitis C elimination.

Ideally, this strategy should be accompanied by the implementation of electronic alerts from microbiology for positive cases together with the sending of notifications to requesting physicians or hepatitis C specialists to avoid the loss of future cases, as well as, together with other micro-elimination strategies in emergency departments, psychiatry or in migrants.[31–33] It is important to note that not all patients can be reached or are willing to seek consultation, so efforts should continue to be made to try to linkage-to-care these individuals to the healthcare system. In addition, it would be beneficial to carry out the strategy again at least every 5 years and assess its effectiveness in reducing the number of patients lost to follow-up.

Conclusion

The active search strategy Relink-C, allowed for the retrieval and treated of a significant number of diagnosed hepatitis C cases that would not have been detected by established procedures in the analysis period. The implementation of one-step diagnosis may not guarantee the complete elimination of diagnosed patients from the system, so it is essential to implement automated alerts and periodic active searches. To ensure the success of these strategies, it is essential to provide physicians (multiple specialties and care levels) with the necessary background information and guidelines. The Relink-C strategy proved to be cost-effective for both full and partial diagnosis and partial diagnosis only, being in line with the 2030 hepatitis C elimination targets.

Conflict of interest

V Aguilera has no conflicts of interest regarding this study.
R González-Grande
MJ Pena has no conflicts of interest regarding this study.
A Bono has no conflicts of interest regarding this study.
R Granados has no conflicts of interest regarding this study.
M Jiménez-Pérez
M Serrano has no conflicts of interest regarding this study.
H Cantero, M Sainz and C González-de-Adalid are employees of Gilead Sciences Spain.
R Domínguez-Hernadez and N Espinoza-Cámac are employees of PORIB and received fees from Gilead Sciences for their consultancy services in relation to the development of this work.

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Author contributions

V Aguilera, R González-Grande, MJ Pena, A Bono, R Granados, M Jiménez-Pérez contributed equally to the data collection and provided information of strategy ReLink-C implementation in Spain. H Cantero, M Sainz, C

González-de-Adalid, and R Domínguez-Hernández contributed to the conception, methodology and design of the study. R Domínguez-Hernández and N Espinoza-Cámac contributed to the interpretation of the data, carried out the adaptation of the data analysis, data processing, the writing-draft and writing-reviews of the manuscript. All authors contributed to the critical revision of the intellectual content and approval of the final version of the manuscript.

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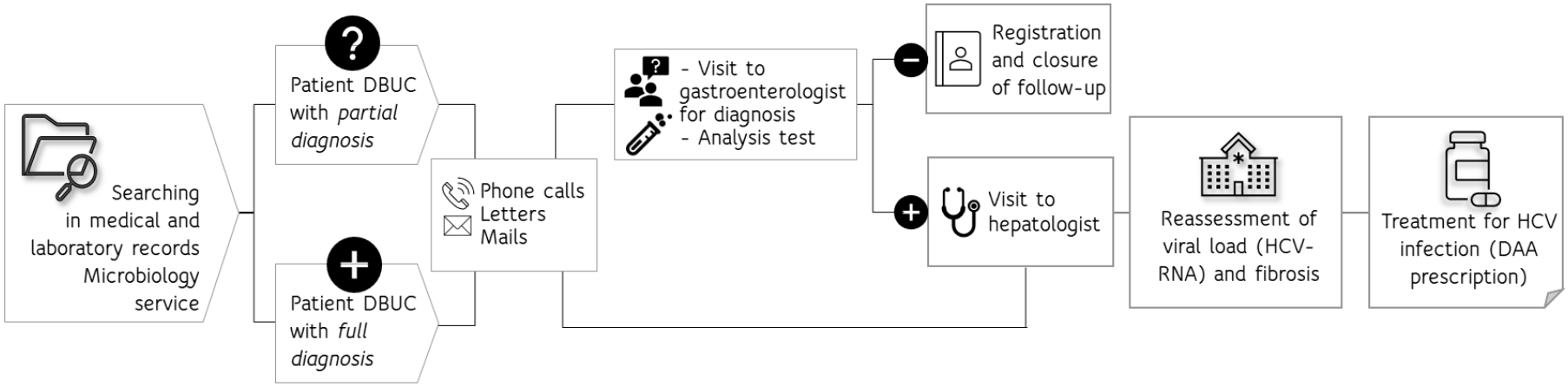
SUPPLEMENTARY

Figure S1. ReLink-C strategy steps scheme.



Abbreviations: DAA, direct-active antiviral; DBUC, diagnosed but unlinked to care; HCV, hepatitis C virus.

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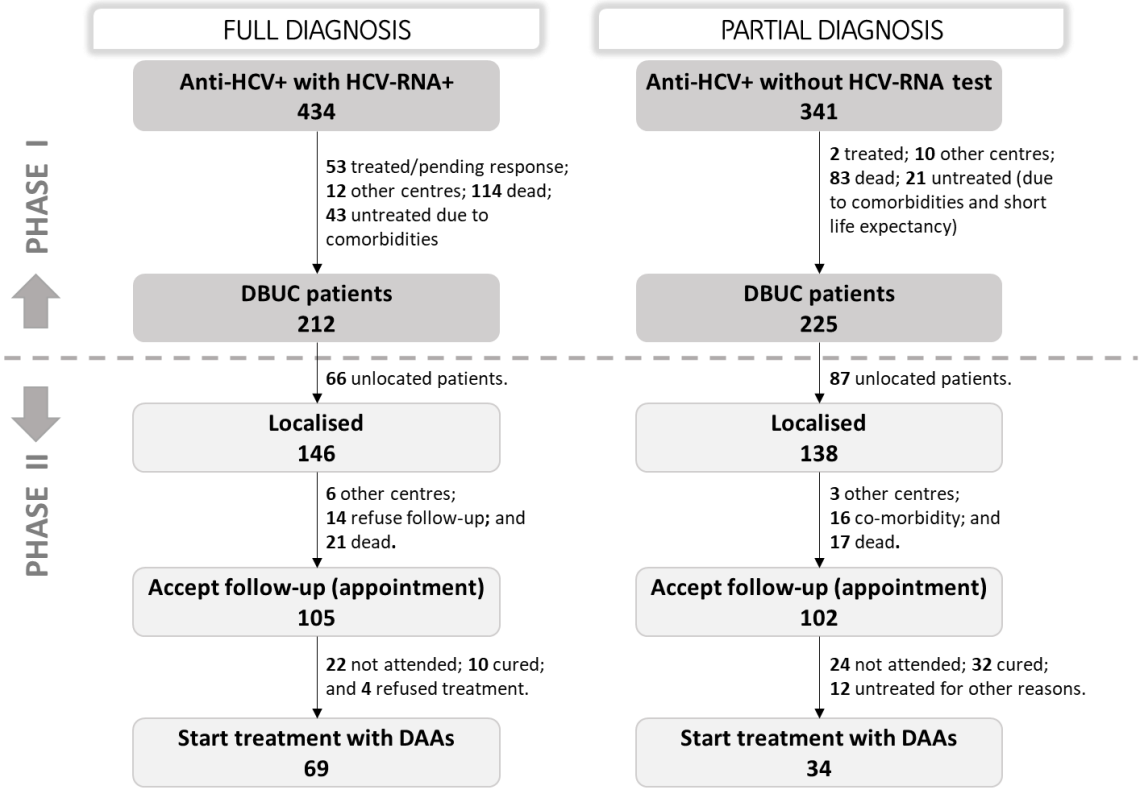
Supplementary 1: Regional University Hospital of Malaga (RUHM) data

Figure S2. Flowchart of ReLink-C strategy in the RUHM of Málaga (2015-2020)



Abbreviations: Anti-HCV+, serology positive to HCV; DAA, direct-active antiviral; DBUC, diagnosed but unlinked to care; HCV, hepatitis C virus; HCV-RNA, HCV viral load; HCV-RNA+, HCV-positive viral load; RUHM, Regional University Hospital of Malaga.

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Table S1. Resource consumption for the search, diagnosis, and linkage of DBUC patients with HCV in RUHM.

Resources	Frequency	Reference
Diagnostic tests, times		
HCV surface antigen	0	Hospital data
HCV viral load (HCV-RNA)	264	
Hemogram	0	
Complete analytics	161	
Genotype	0	
Liver elastography	117	
Abdominal ultrasound	16	
Specialists visit, times		
Day Hospital (nursing)	161	
Hepatology - First visits	161	
Hepatology - Successive visits	103	
Hepatology telephone consultation, times	32	
Time spent searching and retrieving patients, hours		
Computer scientists	6 (search)	
Statisticians	24 (search)	
Data Manager	1181 (search) 218 (location)	
Hepatologists	1181 (search)	

Abbreviations: DBUC, diagnosed but unlinked to care; HCV, hepatitis C virus; HCV-RNA, HCV viral load; RUHM, Regional University Hospital of Malaga.

Table S2. Total hours and per patient for search and retrieval in RUHM (Málaga).

Parameter	Patients (n)	Hours (total)	Hour/patient (media)
Search of DBUC patients	775	2392	3
Location of DBUC patients	437	218	0.5

Abbreviations: DBUC, diagnosed but unlinked to care; RUHM, Regional University Hospital of Malaga.

Table S3. Clinical characteristics of HCV-RNA+ patients retrieved with ReLink-C strategy in the RUHM (Málaga).

Parameters	Full diagnosis (n=117*)	Partial diagnosis (n=34*)
Men, n (%)	73 (62.4)	15 (44%)
Age, median (± SD)	54.5 (34-91)	57.5 (34-87)
Fibrosis stage, n (%)		
F0	16 (13.7)	20 (58.8)
F1	71 (60.7)	6 (17.6)
F2	14 (12.0)	3 (8.8)
F3	4 (3.4)	4 (11.7)
F4	12 (10.3)	1 (2.9)

*Characteristics of patients for whom information is available.
Abbreviations: F, fibrosis stage; HCV-RNA+, HCV-positive viral load; RUHM, Regional University Hospital of Malaga.

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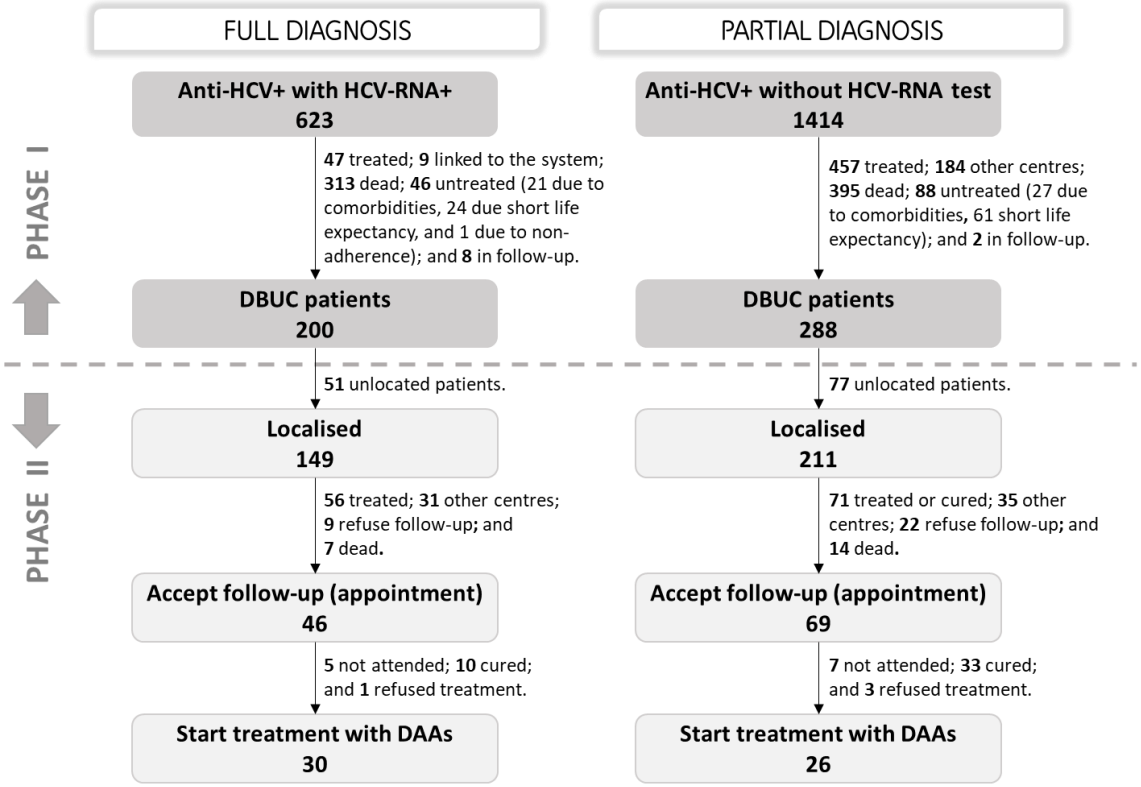
Supplementary 2: University and Polytechnic Hospital La Fe (UHLF) of Valencia data

Figure S3. Flowchart of ReLink-C strategy in the UHLF of Valencia (2010-2020)



Abbreviations: Anti-HCV+, serology positive to HCV; DAA, direct-active antiviral; DBUC, diagnosed but unlinked to care; HCV, hepatitis C virus; HCV-RNA, HCV viral load; HCV-RNA+, HCV-positive viral load; UHLF, University and Polytechnic Hospital La Fe (Valencia).

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Table S4. Resource consumption for the search, diagnosis, and linkage of DBUC patients with HCV in UHLF (Valencia) for full and partial diagnosis.

Resources	Frequency	Reference
Diagnostic tests, times		
HCV serology	34	Hospital data
HCV viral load (HCV-RNA)	162	
Complete analytics	103	
Genotype	103	
Liver elastography	59*	
Abdominal ultrasound	20	
Specialists visit, times		
Hepatology - First visits	103	
Hepatology - Successive visits	56	
Nurse telephone consultation (Rescheduling appointments, attending tests and treatment)	1,020	
Time spent searching and retrieving patients, hours		
Microbiologists	6 (search)	
Hepatologists	40 (search) 243 (location)	

Abbreviations: DBUC, diagnosed but unlinked to care; HCV, hepatitis C virus; HCV-RNA, HCV viral load; UHLF, University and Polytechnic Hospital La Fe (Valencia).
*Staging of fibrosis by FIB 4 to 13 patients

Table S5. Total hours and per patient for search and retrieval in UHLF (Valencia)

Parameter	Patients (n)	Hours (total)	Hour/patient (media)
Search of DBUC patients	2037	46	1.35 minutes
Location of DBUC patients	488	243	30 minutes

Abbreviations: DBUC, diagnosed but unlinked to care; UHLF, University and Polytechnic Hospital La Fe (Valencia).

Table S6. Clinical characteristics of HCV-RNA+ patients retrieved with ReLink-C strategy in the UHLF (Valencia).

Parameters	Full diagnosis (n=72)*	Partial diagnosis (n=28)*
Men, n (%)	41 (56.9)	16 (57.1)
Age, median (range)	57 (25-84)	58 (42-80)
Fibrosis stage, n (%)		
F0	31 (43.1)	10 (35.7)
F1	9 (12.5)	3 (10.7)
F2	12 (16.7)	6 (21.4)
F3	7 (9.7)	5 (17.9)
F4	13 (18.1)	4 (14.3)

*Characteristics of patients for whom information is available
Abbreviations: F, fibrosis stage; HCV-RNA+, HCV-positive viral load; UHLF, University and Polytechnic Hospital La Fe (Valencia).

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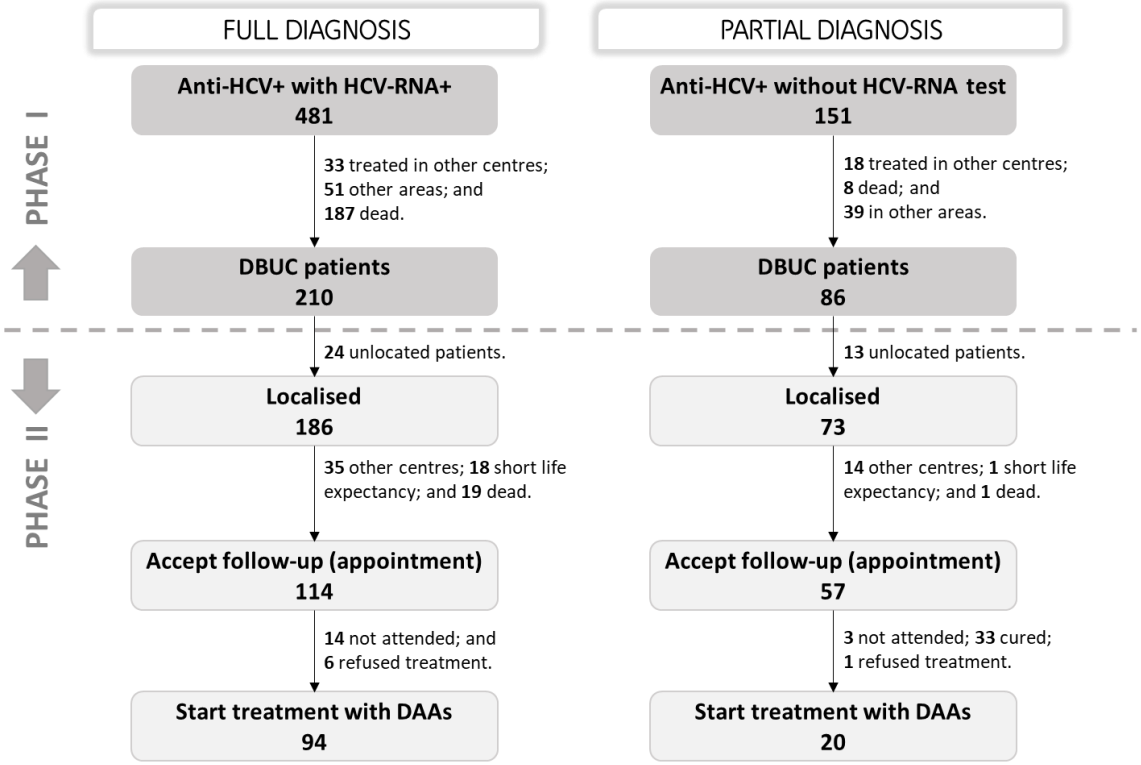
Supplementary 3: University Hospital Doctor Negrin (UHDN) in Gran Canaria data.

Figure S4. Flowchart of ReLink-C strategy in the UHDN of Gran Canarias (2015-2020)



Abbreviations: Anti-HCV+, serology positive to HCV; DAA, direct-active antiviral; DBUC, diagnosed but unlinked to care; HCV, hepatitis C virus; HCV-RNA, HCV viral load; HCV-RNA+, HCV-positive viral load; UHDN: University Hospital Doctor Negrin (Gran Canaria).

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Table S7. Resource consumption for the search, diagnosis, and linkage of DBUC patients with HCV in the UHDN (Gran Canaria).

Resources	Frequency	Reference
Diagnostic tests, times		
HCV serology	0	Hospital data
HCV viral load (HCV-RNA)	268	
Hemogram	154	
Complete analytics	154	
Genotype	154	
Liver elastography	138	
Abdominal ultrasound	43	
Endoscopy	28	
Specialists visit, times		
Hepatology - First visits	154	
Hepatology - Successive visits	114	
Time spent searching and retrieving patients, hours		
Microbiologists	14 (search)	
Hepatologists	148 (location)	

Abbreviations: DBUC, diagnosed but unlinked to care; HCV, hepatitis C virus; HCV-RNA, HCV viral load; UHDN, University Hospital Doctor Negrin (Gran Canaria).

Table S8. Total hours and per patient for search and retrieval in the UHDN (Gran Canaria).

Parameter	Patients (n)	Hours (total)	Hour/patient (media)
Search of DBUC patients	632	14.3	1.35 minutes
Location of DBUC patients	296	148	30 minutes

Abbreviations: DBUC, diagnosed but unlinked to care; UHDN: University Hospital Doctor Negrin (Gran Canaria).

Table S9. Clinical characteristics of HCV-RNA+ patients retrieved with ReLink-C strategy in the UHDN (Gran Canaria).

Parameters	Full diagnosis (n=138*)	Partial diagnosis (n=24*)
Men, n (%)	109 (79.0)	19 (79.2)
Age, mediana (± SD)	54.5 (7.7)	54.0 (7.9)
Fibrosis stage, n (%)		
F0 – F1	63 (45.6)	10 (41.7)
F2	32 (23.2)	6 (25.0)
F3	15 (10.9)	2 (8.3)
F4	28 (20.3)	6 (25.0)

*Characteristics of patients for whom information is available.

Abbreviations: F, fibrosis stage; HCV-RNA+, HCV-positive viral load; UHDN: University Hospital Doctor Negrin (Gran Canaria).

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Table S10. Unit costs in the search, diagnosis, and linkage of patients with HCV

Resources	Unit cost (€, 2024)	Reference
Diagnostic tests		
HCV serology	€4.29	García-Herola A, 2021[24]
HCV viral load (HCV-RNA)	€42.67	García-Herola A, 2021[24]
Complete analytics	€27.77	García-Herola A, 2021[24]
Genotype	€44.34	García-Herola A, 2021[24]
Liver elastography	€46.49	García-Herola A, 2021[24]
Abdominal ultrasound	€65.08	García-Herola A, 2021[24]
Endoscopy	€127.14	García-Herola A, 2021[24]
Specialists visit		
Hepatology - First visits	€80.34	García-Herola A, 2021[24]
Hepatology - Successive visits	€49.47	García-Herola A, 2021[24]
Hepatology telephone consultation	€9.50	Assumption [a]
Nurse telephone consultation	€9.50	eSalud[23]
Cost per hora		
Hepatology	€30.81 - €37.61	Wage remuneration[20–22]
Microbiologist	€30.81 - €37.61	Wage remuneration[20–22]
Computer scientists	€14.95 - €20.01	Wage remuneration[20–22]
Statisticians	€14.95 - €20.01	Wage remuneration[20–22]
Data Manager	€24.04 - €28.17	Wage remuneration[20–22]

a. In the absence of information, the cost has been assumed to be the same as a telephone nursing consultation.

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