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ORIGINAL ARTICLE

Assessing the rate of non-linkage to care and identifying barriers in individuals living with hepatitis B. Results of the LINK-B study

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Abstract

Background & Aims: Hepatitis B infection is the most frequent cause of chronic hepatitis and liver cancer worldwide. Active searching for individuals with chronic hepatitis B has been proposed as a strategy to achieve the elimination of this virus. The primary aim of this study was to link to specialists HBsAg-positive individuals detected in a laboratory database and to characterize individuals who were not linked to care.

Methods: We performed a retrospective–prospective evaluation of all HBsAg-positive serum samples identified in the central laboratory of the Northern Barcelona area between January 2018 and June 2022. After reviewing the patients' clinical charts, all those not linked to care were given an appointment with a specialist.

Results: Medical records of 2765 different HBsAg-positive serum samples were reviewed and 2590 individuals were identified: 844 (32.6%) were not linked to a specialist, 653 were candidates for linkage, and 344 attended the specialist visit. The two main reasons why they were not under specialist care were administrative issues, such as living in another region (12.1%) and lacking contact details (4.1%), and low life expectancy (2.8%). Individuals who did not attend their scheduled visit were mainly young [38.1 ± 12.9 vs. 44.0 ± 14.0 ($p < .001$)], non-White European [75.3% vs. 58.1% ($p < .001$)] and men [70.7% vs. 56.4% ($p < .001$)].

Conclusions: One in every three HBsAg-positive individuals in our setting was not currently under specialist care. Of particular note, half of them had never attended a specialist consultation, an essential step for evaluating the disease and starting therapy in some countries.

Abbreviations: AEMPS, Spanish Agency of Medicines and Medical Devices; ALT, Alanine aminotransferase; Anti-HBe, anti-hepatitis B e antibody; Anti-HCV, anti-hepatitis C virus antibody; Anti-HDV, anti-hepatitis D virus antibody; Anti-HIV, anti-human immunodeficiency virus antibody; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; EASL, European Association for the Study of the Liver; FIB-4, Fibrosis-4 index for liver fibrosis; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; OR, odds ratio; PCP, primary care physician; PWID, persons who inject drugs; TE, transient elastography; WHO, World Health Organization.

KEYWORDS
access to care, barriers, cascade of care, hepatitis B, linkage to care, retention in care

1 | INTRODUCTION

Hepatitis B virus (HBV) infection remains a major global health concern.[1] In 2019, an estimated 296 million people worldwide were living with hepatitis B.[2] Chronic HBV infection can lead to cirrhosis and hepatocellular carcinoma (HCC) and has an associated mortality rate of 820 000 deaths per year.[2,3] Spain is a low-endemic country, with a 0.4% prevalence of hepatitis B surface antigen (HBsAg).[4] Although Spain has a well-established vaccination programme for newborns and adolescents, as well as effective treatment,[5] HBV infection is still detected, particularly in migrants from high-incidence countries and individuals at risk of the infection, such as people who use injected drugs and men who have sex with men.[6] HBV infection can remain asymptomatic for many years, and it is estimated that 90% of people living with the disease are not aware of their condition and, consequently, not linked to care.[2]

The World Health Organization (WHO) has set up a viral hepatitis elimination programme with the goals of reducing 90% of new hepatitis B and C infections and 65% of liver-related mortality by 2030.[7] In recent years, several strategies have been developed for this purpose, such as national plans against hepatitis C, with micro-elimination approaches focused on high-risk populations.[8] Because of these efforts, at least nine high-income countries are now on track to achieve the WHO hepatitis C goals by 2030.[9] However, the scenario for hepatitis B is less favourable.[10] Recent estimations predict that none of the participating countries will eliminate hepatitis B by this time point, a fact that highlights the importance of implementing strategies similar to those used in hepatitis C.[11,12] One proposed intervention is active searching for people with undiagnosed HBV infection and simplifying access to care. The aim of this study, named LINK-B, was to link to specialist care all HBsAg-positive individuals identified in the database of a central laboratory covering a large healthcare area. Secondary aims were to characterize patients who were not receiving specialist follow-up and to determine the barriers to successful linkage to care.

Key points

- One in every three people living with hepatitis B in our setting was not linked to specialist care and received incomplete monitoring.
- Individuals not linked to specialist care were mainly young, non-White European men.
- The LINK-B study retrieved 40% of hepatitis B cases not linked to a specialist and enabled treatment of patients who were not candidates for therapy initially.

2 | MATERIALS AND METHODS

2.1 | Study design

We performed a retrospective–prospective evaluation of all adults (≥18 years of age) testing positive to HBsAg in the central laboratory of the Northern Barcelona (Spain) health area between January 2018 and June 2022. Northern Barcelona has an integrated public healthcare system including 16 primary care centres, three drug addiction centres, and an academic hospital with a catchment population of 450 000 inhabitants. At their discretion, primary care physicians (PCPs) and other healthcare providers refer patients with chronic hepatitis B infection to specialists (i.e. mainly gastroenterologists and hepatologists) to complete the HBV diagnosis and evaluate the indication for therapy. The conventional referral circuit from primary care involves an electronic request by the PCP that results in a hospital appointment, with patients being informed of the date by phone calls and letter. After the specialist evaluation and depending on their clinical status, patients are prescribed treatment or not, and continue follow-up in primary care or at the hospital.

The study, designed in 2021, had a retrospective part (January 2018 to December 2020) and a prospective part (January 2021 to June 2022). The electronic medical records of all individuals who had an HBsAg-positive laboratory determination recorded in our database during the study period were reviewed by a physician or nurse. In participants with consecutive HBsAg determinations, we only counted the first positive test.[13] Individuals were excluded if they were diagnosed with self-limited acute hepatitis, HBsAg tested weakly positive and was not confirmed in a following determination: they had insufficient data for the study, they moved into another region, or they died during the retrospective phase. A nurse contacted HBsAg-positive individuals who were not currently linked to care by phone (maximum of five attempts) and, in case of no response, by letter. Linkage to care was defined when an individual retrieved from the laboratory records successfully attended an initial evaluation or a follow-up visit with a specialist. These participants underwent clinical assessment, laboratory analyses, and complementary tests at the physician's discretion, including transient elastography (TE), abdominal ultrasound, and liver biopsy. Participants were classified into the various stages of HBV infection according to the EASL guidelines, and those meeting the criteria for antiviral treatment started therapy.[1] Subsequent follow-up visits were scheduled by the attending specialist. HBsAg-positive individuals who were appropriately linked to care (follow-up visit every 6 months or at least once per year) did not undergo any additional interventions.

The study was approved by the Ethics Committee of Vall d'Hebron Hospital (PR(AG)201/2021; 26/03/2021) and the Spanish Agency of Medicines and Medical Devices (AEMPS), and was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. Informed consent for participation was waived with the approval of the ethics committee because no interventions other than those of regular clinical practice were carried out. All data were anonymized.

2.2 | Methods

The following parameters were collected for all participants: age, sex, date of blood sample, centre, and type of healthcare provider. In HBsAg-positive patients who were not linked to care, additional data were collected: demographic, clinical, and laboratory parameters, potential cause of non-linkage to care, risk factors for HBV infection, comorbidities, and infection status. Ultrasound, TE, and liver biopsy results were recorded. The degree of fibrosis, development of liver decompensation (ascites, variceal bleeding, hepatic encephalopathy, and hepatocellular carcinoma), indication for liver transplantation, and liver-related death were recorded. Data regarding HBV therapy were also collected. Data collected from the medical records were confirmed and updated during the study visit.

Laboratory parameters collected included platelet count, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, hepatitis B e antigen (HBeAg), hepatitis B antigen e antibodies (anti-HBe), HBV DNA, anti-hepatitis D virus IgG antibodies (anti-HDV), HDV RNA, anti-hepatitis C virus (anti-HCV) antibodies, HCV RNA, and anti-HIV antibodies. Viral load was measured in all individuals testing anti-HDV, anti-HCV, and anti-HIV-positive. HDV RNA was quantified with an in-house technique.[14] Liver fibrosis indices, such as FIB-4, and the AST to platelet ratio index (APRI) were also recorded.

2.3 | Statistical analysis

Quantitative variables were analysed with the Mann–Whitney *U* test or the Student *t* test, as appropriate, and expressed as mean and standard deviation. Categorical variables were compared using the chi-square or Fisher's exact test, when frequencies were less than 5%, and expressed as frequency and percentage. Results were considered statistically significant at *p*-values lower than .05. All statistical analyses were performed using IBM SPSS, version 26.0 (SPSS Inc., Armonk, NY, USA).

3 | RESULTS

In total, 2765 HBsAg-positive individuals were identified during the study period; 175 were excluded because of one of the following conditions: death ($n=96$), a later HBsAg-negative determination ($n=56$), or age younger than 18 years ($n=23$). Thus, 2590 individuals were included: 1746 (67.4%) were currently linked to a specialist for HBV follow-up, and 844 (32.6%) were not. A flow chart depicting the LINK-B retrieval circuit from inclusion to treatment is provided in Figure 1.

3.1 | Baseline characteristics of individuals not linked to specialist care

Of the 844 participants not linked to specialist care, 191 (22.6%) were not considered candidates for the following reasons: living in another region ($n=102$, 12.1%), lacking contact details ($n=35$, 4.1%), low life expectancy ($n=24$, 2.8%), or discharge from specialist care to continue HBV follow-up in primary care ($n=30$, 3.6%) (Figure 1).

Patients who were not linked were more often younger (mean age 41.7 ± 15.4 vs. 45.8 ± 15.5 years, $p<.001$), men (65.2% vs. 61.7%, $p=.047$), HBeAg negative (94.1% vs. 87.5%, ($p<.001$), and less often tested for HBV DNA (38.4% vs. 66.4% $p<.001$) than those linked to care. Moreover, individuals who were not linked were less often coinfected with hepatitis D (4.0% vs. 12.6%; $p=.001$), hepatitis C (2.9% vs. 4.6%; $p=.05$), or HIV (0.4% vs. 2.6%; $p=.004$), and there were fewer showing FIB-4 scores >3.25 (2.5% vs. 6.0%, $p=.001$) and APRI scores >1.5 (1.3% vs. 3.8%, $p=.001$). Baseline characteristics are shown in Table 1.

There were two main reasons why the 844 patients were not linked: they did not attend the specialist consultation ($n=413$,

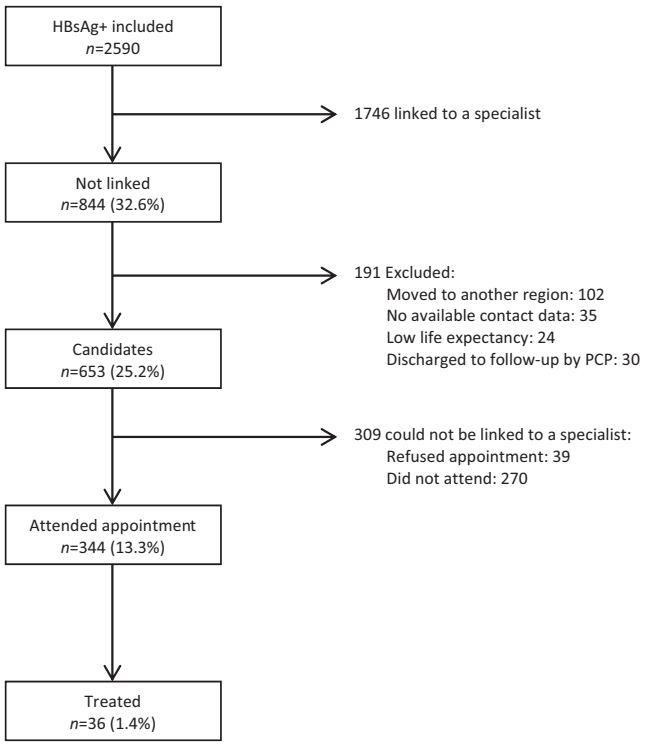

FIGURE 1 Flow chart depicting the LINK-B retrieval circuit. HBsAg, hepatitis B surface antigen.

48.9%) and the PCP did not perform the referral ($n = 299$, 35.4%) (Figure 2). The medical records showed that 430 (50.9%) had previously undergone specialist follow-up, and 414 (49.1%) had never been seen by a specialist. Individuals who had never been linked were mainly tested in primary care ($n = 280$, 67.3%). Baseline characteristics of the never linked and previously linked patients are shown in Table 2. There were no significant differences between these groups.

3.2 | Barriers to linkage to specialist care

Among the 653 participants contacted, 344 attended the specialist consultation. Of the remaining 309 patients, 39 (5.9%) refused the appointment, and 270 (41.3%) did not attend (Figure 1). Participants who were not seen were more often young, non-White European, men ($p < .001$ in all characteristics). The baseline characteristics of these individuals are shown in Table 3.

TABLE 1 Baseline demographic and clinical characteristics of 2590 HBsAg-positive individuals by linkage to specialists status.

	Linked to a specialist $n = 1746$	Not linked to a specialist $n = 844$	p
Age, years, mean	45.8 ± 15.5	41.7 ± 15.4	**.000******
Sex, male, *n* (%)	1077 (61.7%)	550 (65.2%)	**.047***
Platelet count, mean, $\times 10^9$/L	228.3 ± 69.6	242.06 ± 69.1	**.000******
AST > 40 IU/L, *n* (%)	238/1425 (16.7%)	91/564 (16.1%)	.408
AST, mean, IU/L	42.5 ± 116.8	35.3 ± 66.6	.062
ALT > 40 IU/L, *n* (%)	340/1620 (21.0%)	139/762 (18.2%)	.065
ALT, mean, IU/L	47.1 ± 176.1	34.3 ± 65.1	.144
HBeAg positive, *n* (%)	169/1353 (12.5%)	41/691 (5.9%)	**.000******
HBV DNA detectable, *n* (%)	891/1159 (76.9%)	301/324 (92.9%)	**.000******
HBV DNA, logIU/mL	2.3 ± 2.0	2.6 ± 1.6	**.000******
Anti-HDV positive, *n* (%)	63/499 (12.6%)	7/174 (4.0%)	**.001*****
HDV RNA detectable, *n* (%)	34/63 (55.7%)	2/7 (28.6%)	**.003****
Anti-HCV positive, n (%)	48/1038 (4.6%)	20/680 (2.9%)	.050
HCV RNA detectable, *n* (%)	2/42 (4.8%)	1/17 (5.9%)	.737
Anti-HIV positive, *n* (%)	18/695 (2.6%)	2/458 (0.4%)	**.004****
FIB-4 > 3.25, *n* (%)	84/1398 (6.0%)	14/559 (2.5%)	**.001*****
FIB-4, mean	1.5 ± 1.6	1.2 ± 0.8	**.000******
APRI > 1.5, *n* (%)	53/1400 (3.8%)	7/560 (1.3%)	**.001*****
APRI, mean	0.5 ± 1.6	0.4 ± 0.5	**.000******

Note: Categorical variables are expressed as *n* (%), and quantitative as mean ± SD. Values in bold are statistically significant $p<0.05$ (*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$).

Abbreviations: ALT, alanine aminotransferase; anti-HCV, anti-hepatitis C virus antibody; anti-HDV, anti-hepatitis D virus antibody; anti-HIV, anti-human immunodeficiency virus antibody; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis-4 index for liver fibrosis; HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; HCV RNA, hepatitis C virus ribonucleic acid; HDV RNA, hepatitis D virus ribonucleic acid.

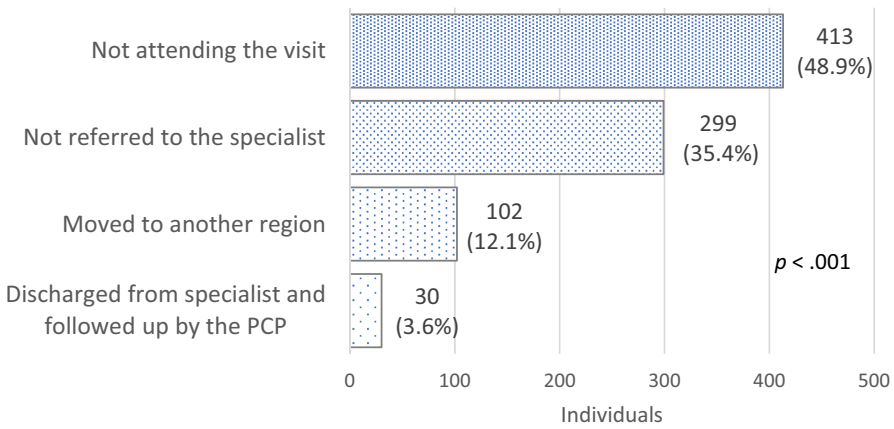

FIGURE 2 Reasons for no linkage to the specialist. PCP, primary care physician.

TABLE 2 Baseline demographic and clinical characteristics of 844 HBsAg-positive individuals currently not linked to a specialist.

	Never linked $n=414$	Previously linked $n=430$	p
Age, years	42.0 ± 15.9	41.3 ± 14.9	.528
Sex, male, *n* (%)	269 (65.0%)	281 (65.3%)	.483
Origin, *n* (%)	323 (77.6%)	351 (82.0%)	
White European	119 (36.8%)	129 (36.8%)	.862
African	89 (27.6%)	109 (31.1%)	
Asian	51 (15.8%)	51 (14.5%)	
Middle East/North Africa	43 (13.3%)	42 (12.0%)	
Latin American	21 (6.5%)	20 (5.7%)	
Platelet count, mean, $\times 10^9$/L	246.9 ± 77.2	237.6 ± 60.6	.059
AST > 40, *n* (%)	34/247 (13.8%)	57/317 (18.0%)	.108
AST, mean, IU/L	30.4 ± 18.1	39.07 ± 87.2	.980
ALT > 40, *n* (%)	60/358 (16.8%)	79/404 (19.6%)	.183
ALT mean, IU/L	30.6 ± 23.1	37.6 ± 86.7	.701
HBeAg positive	15/359 (4.2%)	26/332 (7.8%)	**.031***
HBV DNA detectable, *n* (%)	111/121 (26.8%)	190/230 (44.2%)	.337
HBV DNA, mean, logIU/mL	2.6 ± 1.5	2.6 ± 1.6	.950
Anti-HDV positive, *n* (%)	5/93 (5.4%)	2/81 (2.5%)	.283
HDV RNA detectable	1/5	1/2	.524
Anti-HCV positive, *n* (%)	8/367 (2.2%)	12/313 (3.8%)	.148
HCV RNA detectable	0/6	1/11	.647
Anti-HIV positive, *n* (%)	1/249 (0.4%)	1/209 (0.5%)	.705
FIB-4 score >3.25, *n* (%)	5/245 (2.0%)	9/314 (2.9%)	.369
FIB-4 score, mean	1.1 ± 0.7	1.2 ± 1.0	.469
APRI score >1.5, *n* (%)	2/246 (0.8%)	5/314 (1.6%)	.336
APRI score, mean	0.3 ± 0.2	0.4 ± 0.7	.539

Note: Categorical variables are expressed as *n* (%), and quantitative as mean ± SD. Values in bold are statistically significant $p<0.05$ ($^*p \le 0.05$, $^{**}p \le 0.01$, $^{***}p \le 0.001$, $^{****}p \le 0.0001$).

Abbreviations: ALT, alanine aminotransferase; anti-HCV, anti-hepatitis C virus antibody; anti-HDV, anti-hepatitis D virus antibody; anti-HIV, anti-human immunodeficiency virus antibody; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis-4 index for liver fibrosis; HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; HCV RNA, hepatitis C virus ribonucleic acid; HDV RNA, hepatitis D virus ribonucleic acid.

3.2.1 | Characteristics of patients linked to specialist care

In total, 344 individuals were successfully linked to a specialist: 256 received the specialist appointment by phone and 88 by letter. In contrast to those who could not be linked, these individuals were more often women (43.6% vs. 29.9%, $p<.001$), older (44.0 ± 14.0 vs. 38.1 ± 12.9, $p<.001$), White Europeans (41.9% vs. 24.7% $p=.046$), and had elevated AST values. Multivariate analysis showed that factors independently associated with a higher likelihood of specialist linkage were female sex (OR = 2.02), age >40 years (OR = 1.79), and ALT values >40 IU/L (OR = 3.04) (Table 3).

At the time of the specialist consultation, all individuals were asymptomatic. None had previous or current liver decompensation or HCC. HBsAg had spontaneously cleared in 20 (5.8%) of the 344 patients seen. Characteristics of the specialist-linked individuals are shown in Table 4. Seventeen (4.9%) had chronic hepatitis D, and 307 were HBV mono-infected. In the latter group, 4 (1.2%) were classified as having HBeAg-positive chronic infection, 12 (3.5%) HBeAg-positive chronic hepatitis B, 263 (76.5%) HBeAg-negative chronic infection, and 22 (6.4%) HBeAg-negative chronic hepatitis B. Six (1.7%) HBeAg-negative patients could not be classified into any stage of the infection. Thirty-six participants started therapy with nucleoside analogues for chronic hepatitis B (Figure 1). In addition, one patient with HBV/HCV coinfection started direct antivirals for chronic hepatitis C.

4 | DISCUSSION

The results of this study showed that one in every three individuals testing HBsAg-positive in our setting was not linked to specialist care. This is a critical factor for monitoring HBV infection and

TABLE 3 Baseline demographic and clinical characteristics of HBsAg-positive individuals by response to retrieval.

	Attended specialist visit $N=344$	Did not attend visit $N=270$	p	Odds Ratio (95% CI)	p value
Age, years, mean Age > 40 years	44.0 ± 14.0	38.1 ± 12.9	**.000******	1.79 (1.09–2.9)	**.020** *
Sex, male, *n* (%)	194 (56.4%)	191 (70.7%)	**.000******	2.02 (1.22–3.33)	**.006** **
Previous linkage to specialist, *n* (%)			.376	–	–
Never linked	169 (49.4%)	137 (50.7%)			
Previously linked	175 (50.9%)	133 (49.3%)			
Origin, *n* (%)	344 (100%)	186 (68.9%)	**.000******	–	–
White European	144 (41.9%)	46 (24.7%)			
African	66 (19.2%)	68 (36.6%)			
Asian	72 (20.9%)	21 (11.3%)			
Middle East/North Africa	36 (10.5%)	41 (22.0%)			
Latin American	26 (7.6%)	10 (5.4%)			
Non-White European, *n* (%)	200 (58.1%)	140 (75.3%)	**.000******	0.48 (0.29–0.82)	**.007****
Platelet count, $\times 10^9$/L, mean	241.4 ± 61.3	241.1 ± 59.0	.945		
AST > 40, IU/L, *n* (%)	44/242 (18.2%)	15/171 (8.8%)	**.005****	–	.290
AST mean, IU/L	32.5 ± 24.4	29.1 ± 16.9	.732		
ALT > 40, IU/L	62/311 (19.9%)	38/247 (15.4%)	.100	3.04 (1.56–5.88)	**.001*****
ALT mean, IU/L	34.3 ± 35.8	28.0 ± 15.7	.383		
HBeAg positive, *n* (%)	16/282 (5.7%)	11/221 (5.0%)	.446	–	–
HBV DNA detectable, *n* (%)	138/144 (40.1%)	90/98 (33.3%)	.330	–	–
HBV DNA mean, logIU/mL	2.7 ± 1.7	2.5 ± 1.4			
Anti-HDV positive, *n* (%)	6/85 (7.1%)	0/48 (0%)	.064	–	–
HDV RNA detectable	2 (33.3%)	–			
Anti-HCV positive, *n* (%)	8/264 (3.0%)	10/223 (4.5%)	.271	–	–
HCV RNA detectable	1 (12.5%)	0/8 (0.0%)			
Anti-HIV positive	0/155 (0%)	0/168 (0%)	–	–	–
FIB-4 mean	1.2 ± 0.8	1.0 ± 0.5	**.001*****	–	–
FIB-4 > 3.25, *n* (%)	4/238 (1.7%)	/171 (1.2%)	.507		
APRI mean	0.3 ± 0.3	0.3 ± 0.2	**.019***	–	–
APRI > 1.5 (F3-4), *n* (%)	2/238 (0.8%)	1/171 (0.6%)	.622		

Note: Categorical variables are expressed as *n* (%), and quantitative as mean ± SD. Values in bold are statistically significant $p<0.05$ (*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$).

Abbreviations: ALT, alanine aminotransferase; anti-HCV, anti-hepatitis C virus antibody; anti-HDV, anti-hepatitis D virus antibody; anti-HIV, anti-human immunodeficiency virus antibody; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis-4 index for liver fibrosis; HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; HCV RNA, hepatitis C virus ribonucleic acid; HDV RNA, hepatitis D virus ribonucleic acid.

indicating therapy, particularly in countries where this treatment can only be given by specialists, as is the case of Spain.[5]

The majority of participants who were not referred to a specialist or did not attend a specialist appointment were young, non-White European, men, HBeAg-negative, and with mild fibrosis. These latter two factors are potential reasons why PCPs did not refer them for specialist care, but it is important to highlight that HBV DNA was analysed in only 38% of cases. The absence of HBV DNA assessment in primary care makes it difficult to determine the stage of chronic HBV infection, which can be a complex task. A comprehensive evaluation and initial monitoring in two or three visits spaced 3–6 months apart are needed to properly classify the disease stage and establish the indication for therapy.[1]

In a similar study performed in Japan, only 14.7% of HBsAg-positive patients were referred to a specialist, mainly those diagnosed in an internal medicine service. The authors stressed the importance of identifying patients who require specialist follow-up and concluded that hepatologists should educate PCPs to promote referral of HBsAg-positive patients.[15] A study among refugees with HBV infection in three U.S. cities also found lower linkage to care, a common observation in underserved populations.[16,17]

TABLE 4 Demographic and clinical characteristics of HBsAg-positive individuals retrieved and linked to care.

	N = 344
Age, years, mean	46.0 ± 13.9
Sex, male, *n* (%)	194 (56.4%)
History of, *n* (%)	
Arterial hypertension	58 (16.9%)
Diabetes	30 (8.7%)
Dyslipidaemia	40 (11.6%)
Psychiatric disorder	39 (11.3%)
Alcohol consumption, *n* (%)	35 (10.2%)
Smoker, *n* (%)	66 (19.2%)
Risk factors, *n* (%)	
Blood transfusion	10 (2.9%)
Tattoo/PWID	6 (1.7%)
Vertical transmission	46 (13.4%)
Sexual risk behaviour	15 (4.4%)
Not recognized	267 (77.6%)
Platelet count mean ($\times 10^9$/L)	233.1 ± 57.0
AST mean (IU/L)	31.1 ± 30.7
AST > 40	43 (12.5%)
ALT mean (IU/L)	32.6 ± 30.4
ALT > 40, *n* (%)	61 (17.7%)
HBeAg positive, *n* (%)	18 (5.2%)
HBV DNA mean (logIU/mL)	2.8 ± 1.5
HBsAg (logIU/mL)	2.8 ± 1.4
HBcrAg	2.7 ± 1.2
Anti-HDV positive	17 (4.9%)
HDV RNA detectable	3 (17.6%)
Anti-HCV positive	8 (2.3%)
HCV RNA detectable	1 (12.5%)
Anti-HIV positive	2 (0.6%)
FIB-4, mean	1.2 ± 1.0
FIB-4 > 3.25, *n* (%)	9 (2.6%)
APRI mean	0.3 ± 0.4
APRI > 1.5 (F3-4), *n* (%)	4 (1.2%)
Transient elastography, *n* (%)	
F0-3 (<12 kPa)	224 (94.9%)
F4 (>12 kPa)	12 (5.1%)

Note: Categorical variables are expressed as *n* (%), and quantitative as mean ± SD.

Abbreviations: ALT, alanine aminotransferase; anti-HCV, anti-hepatitis C virus antibody; anti-HDV, anti-hepatitis D virus antibody; anti-HIV, anti-human immunodeficiency virus antibody; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis-4 index for liver fibrosis; HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; HCV RNA, hepatitis C virus ribonucleic acid; HDV RNA, hepatitis D virus ribonucleic acid; PWID, persons who inject drugs.

An important finding of our study is that a proportion of patients who were initially not considered for therapy had criteria for treatment at specialist follow-up, as has been shown in previous reports.[18,19] Thirty-six patients started therapy after the specialist consultation, and this would not have happened if they had only been attended in primary care.

Our results are useful to understand the reasons why individuals testing positive to HBV lack specialist care in a country with a health system providing universal coverage. Several barriers can hinder the linkage to care in the HBV-positive population: lack of awareness of the potential severity of the condition, stigma and discrimination, financial constraints, limited access to healthcare services, migrant and transient status, and language barriers.[2] Some of these factors, such as financial constraints and limited access to health care, did not apply to our population, as health care is provided to all residents with minimal or no cost. We did, however, find a lack of knowledge of the disease in both patients and referring PCPs in 49% of cases. Many people with hepatitis B are unaware of their infection status or the potential consequences of the disease. Lack of knowledge about available healthcare services and the importance of seeking care can prevent individuals from taking appropriate action. Around half the patients contacted for referral during LINK-B refused or did not attend the appointment. It is reasonable to think that a number of these patients would have accepted referrals if they had known about the potential severity of their condition.

In one-third of patients who were not linked, PCPs had not performed the referral. In our primary care centres, specialist referral of HBV-positive patients is left to the discretion of the attending PCP. The large percentage of non-linkage due to this factor indicates that some educational activity is warranted among PCPs to raise awareness of the benefits of specialist referral in this disease. Although all newly linked patients in the present study were asymptomatic, 36 had criteria to start treatment based on the specialist assessment, thus supporting the value of referral.

Mobility and lack of contact details can disrupt the continuity of care in individuals with hepatitis. In our study, up to 16% could not be linked to care due to administrative reasons, showing the importance of recording changes in residence and updating contact information, particularly phone numbers and addresses.[20]

The results found here suggest that the policy of specialist referral to receive HBV therapy in our country may be a potential barrier that hinders some patients from accessing HBV care. To address this, a more community-based approach is needed, in line with the 2022 WHO Consolidated Guidelines[21] for viral hepatitis. These guidelines emphasize the importance of overcoming structural barriers in all settings and decentralizing care to ensure equitable services. Simplifying the HBV care pathway is essential for improving the diagnosis and treatment of this disease. Identification of certain barriers during the study has prompted us to develop a set of interventions aimed at facilitating linkage, which are currently under evaluation. A phone app has been created for HBV patients to record their medication, to provide information through a survey, and to facilitate direct specialist contact. An educational leaflet has been designed and distributed in our outpatient clinic. Finally, we have launched a website for PCPs with information on HBV infection and a way to contact us for additional guidance.

The main limitation of our study is the retrospective design in the first period, which limited the collection of some potentially relevant

variables. Nonetheless, the study has the advantages of including a large number of participants from a European centre with a substantial immigrant population.

In summary, more than one-third of HBsAg-positive individuals are not linked to specialist care in our setting. The LINK-B strategy retrieved 40% of these patients for a specialist consultation. By addressing the barriers to linkage and implementing targeted interventions, we can enhance care for individuals with hepatitis B and achieve better health outcomes.

AUTHOR CONTRIBUTIONS

Conceptualization, Ana Barreira-Díaz, Ariadna Rando, Mar Riveiro-Barciela, Francisco Rodriguez-Frias, Rafael Esteban, Maria Buti; methodology, Anna Feliu-Prius, Ana Barreira-Díaz, Ariadna Rando, Elena Vargas-Accarino, Adriana Palom, Judit Vico-Romero, Juan C. Ruiz-Cobo; software, Mar Riveiro-Barciela; formal analysis, Mar Riveiro-Barciela; investigation, Ana Barreira-Díaz, Anna Feliu-Prius, Mar Riveiro-Barciela, Maria Buti; resources, Maria Buti; data curation, Ana Barreira-Díaz, Anna Feliu-Prius, Elena Vargas-Accarino, Mar Riveiro-Barciela, Maria Buti; writing – original draft preparation, Anna Feliu-Prius, Ana Barreira-Díaz, Elena Vargas-Accarino, Maria Buti.; writing – review and editing, Mar Riveiro-Barciela, Maria Buti; visualization, Mar Riveiro-Barciela, Maria Buti; supervision, Maria Buti; project administration, Maria Buti; funding acquisition, Maria Buti. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

MB has served as a speaker and advisory board member for Gilead, Roche, and Arbutus. MR-B has served as a speaker for AbbVie and Gilead. RE has served as a speaker and advisory board member for Gilead, Roche, and Arbutus.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL

The study was approved by the Ethics Committee of Vall d'Hebron Hospital (PR(AG)201/2021; 26/03/2021) and the Spanish Agency of Medicines and Medical Devices (AEMPS) and was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements.

PATIENT CONSENT

Informed consent for participation was waived with the approval of the Ethics Committee because no interventions other than those of regular clinical practice were carried out. All data were anonymized.

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