

Chronic hepatitis D associated with worse patient-reported outcomes than chronic hepatitis B

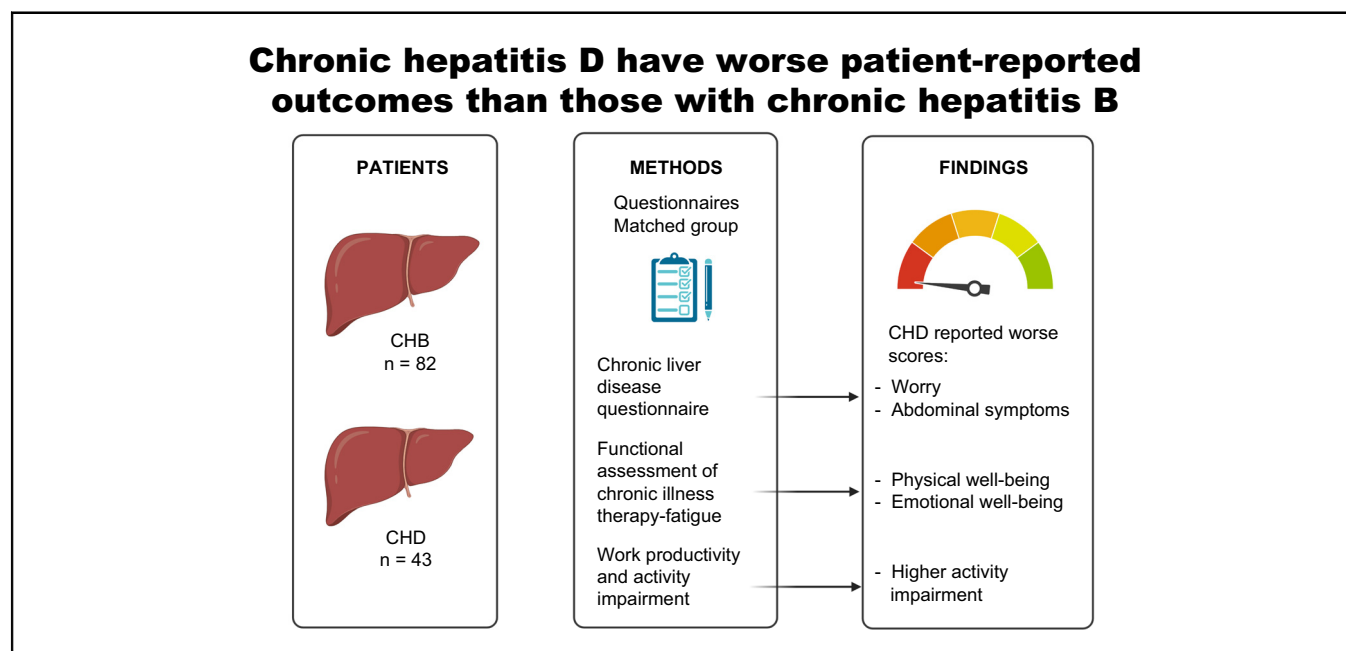
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Graphical abstract



Highlights

- Patient-reported outcomes (PROs) have been studied in patients with chronic hepatitis B and C.
- There are no data on PROs for chronic hepatitis D.
- Several scores of health-related quality of life are worse in patients with chronic hepatitis D than in those with chronic hepatitis B.
- PROs are useful for evaluation of quality of life in clinical trials during and after treatment.

Lay summary

Chronic hepatitis D (CHD) is a viral disease that causes rapid evolution to liver cirrhosis, amongst other severe complications, when compared to patients with chronic hepatitis B (CHB). Health-related quality of life in chronic hepatitis C and CHB has been reported widely, but no studies have been performed on patient-reported outcomes in patients with CHD. Results showed that CHD patients reported worse outcomes in psychological domains such as worry and emotional well-being, as well as in physical domains such as abdominal symptoms, physical well-being, and activity impairment in comparison with patients with CHB.

Chronic hepatitis D associated with worse patient-reported outcomes than chronic hepatitis B



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Background & Aims: Health-related quality of life (HRQoL) determined by patient-reported outcomes (PROs) is impaired in chronic hepatitis B (CHB) and C patients, but there are no data regarding patients with chronic hepatitis D (CHD). The aim of this study was to assess PRO scores in untreated patients with CHD and compare them with those obtained for patients with CHB.

Methods: Patients with CHD completed 3 PRO instruments (Chronic Liver Disease Questionnaire [CLDQ], Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-F], and Work Productivity and Activity Impairment [WPAI]), and the results were compared with those of patients mono-infected with CHB.

Results: In total, 125 patients were included: 43 with CHD and 82 with CHB. Overall, baseline PROs showed differences between both groups. Several assessments, such as the worry score from CLDQ ($p = 0.0118$), functional well-being from FACIT-F ($p = 0.0281$), and activity impairment from WPAI ($p = 0.0029$) showed a significant trend to worse scores in patients with CHD than with CHB. In addition, the linear regression model supports the finding that having CHD as opposed to having CHB was a predictor of a higher worry score (CLDQ) and a higher activity impairment (WPAI).

Conclusions: In this first assessment in CHD, PROs recorded in patients with CHD showed a significant impairment in some domains of HRQoL questionnaires in comparison with those with CHB. Studies in larger cohorts with lengthier follow-up are needed to fully assess patient-reported quality of life over the course of CHD.

Lay summary: Chronic hepatitis D (CHD) is a viral disease that causes rapid evolution to liver cirrhosis, amongst other severe complications, when compared to patients with chronic hepatitis B (CHB). Health-related quality of life in chronic hepatitis C and CHB has been reported widely, but no studies have been performed on patient-reported outcomes in patients with CHD. Results showed that CHD patients reported worse outcomes in psychological domains such as worry and emotional well-being, as well as in physical domains such as abdominal symptoms, physical well-being, and activity impairment in comparison with patients with CHB.

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Introduction

Chronic liver diseases, particularly liver cirrhosis and hepatocellular carcinoma, have been associated with reductions in health-related quality of life (HRQoL) and poorer patient-reported outcomes (PROs).^{1–3} Regardless of the aetiology of liver disease, patients with chronic viral hepatitis, alcoholic liver disease, or fatty liver disease can have impaired HRQoL, and this poses a significant economic burden on society.^{4,5}

Health-related outcomes and PROs have both been extensively investigated in patients with chronic hepatitis C (CHC).^{6,7}

Several studies performed in different countries showed that PRO scores are impaired during the natural course of HCV infection and are poorer in patients with liver cirrhosis than in those with mild fibrosis.^{8–10} Hepatitis C therapy based on interferon demonstrated a decline in quality of life during therapy¹¹ and a later improvement when HCV elimination was achieved.^{12,13} Therapy based on oral direct-acting antivirals (DAAs) has dramatically changed the management of CHC patients, providing effective treatment with improvements in HRQoL during and after therapy.^{14,15} A recent study found that chronic hepatitis B (CHB) and CHC patients had worse PRO scores when they tested positive for viraemia, than after viral suppression or sustained virological response, when there was a substantial improvement.¹⁶

Chronic hepatitis D (CHD) is the most severe form of chronic viral disease,¹⁷ often leading to liver cirrhosis.^{18,19} HDV requires the simultaneous presence of HBV to be infectious and fully

Keywords: Viral hepatitis; Health-related quality of life; Chronic Liver Disease Questionnaire; Functional Assessment of Chronic Illness Therapy–Fatigue; Work Productivity Activity Impairment.

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express its pathogenicity and, therefore, HDV infection always occurs in the presence of HBV.²⁰ Worldwide, 5% of chronically infected HBV patients are also infected with HDV, which yields an estimated 20 million people with HDV infection.^{21,22} Current therapy for patients with CHD is interferon alpha (IFN α) or pegylated interferon alpha (peg-IFN α).^{23,24} Recently, a new drug, bulevirtide, a first class entry inhibitor has obtained conditional authorisation by the European Medicines Agency (EMA) to treat hepatitis D.²⁵

Individuals with CHD are 2–3 times more prone to develop liver cirrhosis than those who are mono-infected by HBV.^{26,27} In addition, among anti-HDV-positive patients, those with active HDV infection are more likely to develop liver cirrhosis and clinical events than those who have persistently undetectable HDV viraemia.²⁸ PROs have not been previously evaluated in patients with CHD, despite the severity of this liver disease.

CHD patients are a heterogeneous population, not only in terms of liver damage, but also regarding their virologic profile, as a result of the interactions between HDV and HBV.²⁹ The majority of patients with CHD have HDV replication and simultaneous suppression of HBV replication either spontaneously or induced by nucleos(t)ide analogues (NAs) treatment. However, a small percentage of them have both HDV and HBV replication or even spontaneously clear HDV replication.²³ The impact of the virologic profile can influence PROs as it occurs in patients with CHB and CHC.

The aims of this study were to compare PROs between patients with CHD and CHB, and also to the impact of the detection of HDV-RNA on PROs.

Patients and methods

Patients

In this study, consecutive HBsAg-positive patients with anti-HDV antibodies were prospectively enrolled in Hospital Vall d'Hebron (Barcelona, Spain) from January 2018 to December 2019. The inclusion criteria were age over 18 years, HBsAg-positive and with presence of anti-HDV (with or without HDV-RNA) for more than 6 months, lack of significant comorbidities or other extra-hepatic manifestations, no antiviral therapy other than NAs for CHB, and a willingness and ability to answer questionnaires in the Spanish language.³⁰ Patients were excluded if they had previous hepatic decompensation, hepatocellular carcinoma, co-infection with HIV or HCV, or other major conditions that could affect quality of life assessment.³¹ A homogenous group of CHB patients testing negative to anti-HDV antibodies and meeting the same inclusion and exclusion criteria was used as the comparator.

In both groups, demographic, educational level, and employment status were collected, as well as clinical and laboratory data (platelet levels, alanine aminotransferase [ALT], aspartate aminotransferase [AST], HBeAg, HDV-RNA, HBV-DNA, liver stiffness measurements, hepatitis B treatment received, clinical events, and history of mental illness). HDV-RNA was quantified using an in-house one-step RT-qPCR. The World Health Organization international standard of quantification was used (with a lower limit of detection [LLOD] of 100 IU/ml and a lower limit of quantification [LLOQ] of 575 IU/ml). HBV-DNA was quantified by a commercial real-time RT-PCR technique with an LLOD of 10 IU/ml and an LLOQ of 20 IU/ml. Liver cirrhosis was defined by clinical and hepatic ultrasound findings, non-invasive markers (fibrosis-4 [FIB-4], AST to platelet ratio index [APRI]),

and hepatic elastography (>13.5 kPa) or liver biopsy showing a fibrosis stage \geq F5 according to the Ishak score.

This study was approved by the Vall d'Hebron Hospital ethics committee (PR[AG]247/2018), and was conducted in compliance with the principles of the Declaration of Helsinki, good clinical practice guidelines, and local regulatory requirements. Patients gave oral consent once the study was explained, and all data were anonymised.

PROs were assessed during the patients' regular visits to the hospital. All instruments were given to the patients to complete on their own just before the visit. To avoid bias in the answers, the site staff and patients were blinded to the most recent analytical results at the time PROs were filled out.

Methods

The PRO questionnaires used were the Chronic Liver Disease Questionnaire (CLDQ), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the Work Productivity and Activity Impairment (WPAI).³²

The CLDQ, the first liver-specific instrument developed, includes 29 items in the following domains: Abdominal Symptoms, Fatigue, Systemic Symptoms, Activity, Emotional Function, and Worry. The CLDQ responses are rated on a scale of 1–7, ranging from having a problem or experiencing a symptom 'all of the time' to 'none of the time', respectively. Thus, higher scores indicate better HRQoL. The original CLDQ was shown to have construct validity in studies on chronic liver diseases.³³

The FACIT-F questionnaire is a fatigue-specific PRO instrument that includes 4 well-being domains (physical, emotional, social, and functional), and a fatigue subscale.³⁴ It is designed as a scale of 0–160, where the higher the score, the higher the HRQoL.

The WPAI-Specific Health Problem is used to evaluate impairment in patients' daily activities and work productivity associated with a specific health problem (in this study, HDV or HBV infection). The Work Productivity Impairment domain is a sum of the Absenteeism (lost hours of work) and Presenteeism (self-reported decreased productivity while working) domains; it is assessed only in employed patients. The Activity Impairment domain focuses on impairment in daily activities other than work and is assessed in all participants regardless of their employment status.³⁵ The sum of specific health problem impairment and impairment attributable to other health reasons is equal to impairment attributable to all health reasons. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

Statistical analysis

Continuous variables are expressed as the mean \pm SD, and categorical variables as n (%). In pairwise comparisons of clinical parameters and PRO scores between groups of interest (e.g. patients with HDV vs. patients with HBV mono-infection, or HDV patients with and without detectable viraemia), the chi-square test and the Mann-Whitney *U* test were used for categorical and continuous parameters, respectively. As mono-infected CHB patients were different from CHD patients by a number of clinical parameters potentially confounding PRO scores, we also utilised a case-control design via selecting matched CHB controls for CHD patients. Matching was done using a propensity score which included age, sex, history of depression or mood disorders, ALT, AST, and platelet count; the propensity scores were then fed to a maximum weight bipartite matching algorithm for

Table 1. Demographic, serologic, virologic, and clinical data of the study cohort.

	Chronic hepatitis D	Chronic hepatitis B	p value
	No. cases = 43	No. cases = 82	
Age, years	47.3 ± 11	51.8 ± 15.3	0.1892
Male sex, n (%)	27 (63)	49 (59.8)	0.7413
Caucasian, n (%)	34 (79)	58 (70.7)	0.3151
Primary education, n (%)	22 (51)	45 (56)	0.6404
Secondary education or higher, n (%)	21 (49)	36 (44)	0.6403
Employed, n (%)	32 (74)	48 (58.5)	0.0789
Housewives, n (%)	9 (21)	9 (11)	0.1396
BMI	26.1 (±3.8)	32.0 (±47.6)	0.6651
ALT, IU/ml	68.4 (±69.0)	29.4 (±28.9)	<0.0001
AST, IU/ml	61.1 (±57.1)	28.5 (±17.9)	<0.0001
Platelets, ×10 ⁹ /L	179.8 (±75.1)	219.9 (±66.5)	0.0061
Hepatic elastography, kPa	10 (6.1-18.1)	4.8 (4.2-5.9)	<0.0001
APRI	1.20 (±1.60)	0.409 (±0.568)	<0.0001
FIB-4	2.61 (±2.95)	1.62 (±1.78)	0.0037
HDV RNA positive, n (%)	26 (60)	0 (0)	-
HBV DNA positive, n (%)	11 (26)	41 (50)	0.0085
HBeAg, n (%)	4 (11)	5 (6)	0.3893
NA treatment, n (%)	27 (63)	32 (39)	0.0115
History anxiety or panic disorder, n (%)	15 (35)	25 (30.5)	0.6167
History depression or mood disorder, n (%)	3 (7)	10 (12.2)	0.3639

All continuous variables are described as median ± IQR, all categorical variables are described as n (%). The Chi-square test and Mann-Whitney *U* test were used for categorical and continuous parameters, respectively. Values of *p* ≤0.05 were considered statistically significant. ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis-4; NA, nucleos(t)ide analogues.

1:1 matching. Values of *p* ≤0.05 were considered statistically significant and *p* <0.10 were considered to indicate a trend (owing to the small sample size).

Patients with CHD patients had significantly higher ALT and AST levels (*p* <0.0001), and higher levels of hepatic elastography (*p* <0.0001), APRI (*p* <0.0001), and FIB-4 (*p* = 0.0037) than those with CHB mono-infection.

Results

Baseline characteristics of patients with CHD and CHB

In total, 125 questionnaires were administered to 43 CHD patients and 82 CHB patients at the inclusion of the study. Baseline demographics, educational status, clinical characteristics, and HDV and HBV serologic and virologic markers are shown in Table 1.

In both groups the majority of patients were male, Caucasians, with a mean age of 50.2±14.2 years, and employed. Patients with primary and secondary or higher educational levels were around 50% in both CHD and CHB groups.

Patient-reported outcomes in patients with CHD and CHB

All patients included completed the Spanish versions of the CLDQ, FACIT-F, and WPAI. The total time needed to fill out the questionnaires ranged from 8 to 15 min.

At study inclusion, the mean CLDQ total score was 5.77 ± 1.06 in patients with CHD and 5.88 ± 0.94 in patients with CHB (*p* = 0.73). Patients with CHD had a significantly worse worry score (*p* = 0.0118) than patients with CHB. There were no other differences in the CLDQ scores for the various domains between these groups.

Table 2. Demographic, serologic, virologic, and clinical data of the matched CHD vs. CHB cohort.

	Chronic hepatitis D	Chronic hepatitis B	p value
	No. cases = 35	No. cases = 35	
Age, years	47.2 ± 12.0	52.0 ± 17.1	0.3351
Male sex, n (%)	22 (62.9)	26 (74.3)	0.3031
Caucasian, n (%)	28 (80.0)	24 (68.6)	0.2740
Employed, n (%)	25 (71.4)	21 (60.0)	0.3138
BMI	25.5 ± 3.3	39.4 ± 73.4	0.1323
ALT, IU/mL	46.3 ± 33.5	40.8 ± 40.7	0.1747
AST, IU/mL	42.9 ± 25.5	36.5 ± 25.0	0.1153
Platelets, ×10 ⁹ /L	178.7 ± 77.3	206.5 ± 54.7	0.0941
APRI	0.932 ± 1.308	0.584 ± 0.829	0.0896
FIB-4	2.48 ± 3.14	1.95 ± 2.45	0.3627
HDV RNA positive, n (%)	19 (54.2)	0 (0)	-
HBV DNA positive, n (%)	10 (28.6)	17 (48.6)	0.0856
HBeAg, n (%)	2 (6.9)	4 (11.8)	0.5118
NA treatment, n (%)	21 (60)	15 (42.9)	0.1513
History anxiety or panic disorder, n (%)	13 (37.1)	9 (25.7)	0.3031
History depression or mood disorder, n (%)	2 (5.7)	2 (5.7)	1.0000

All continuous variables are described as median ± IQR, all categorical variables are described by number and percentage. The Chi-square test and Mann-Whitney *U* test were used for categorical and continuous parameters, respectively. Values of *p* ≤0.05 were considered statistically significant. ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis-4; NA, nucleos(t)ide analogues.

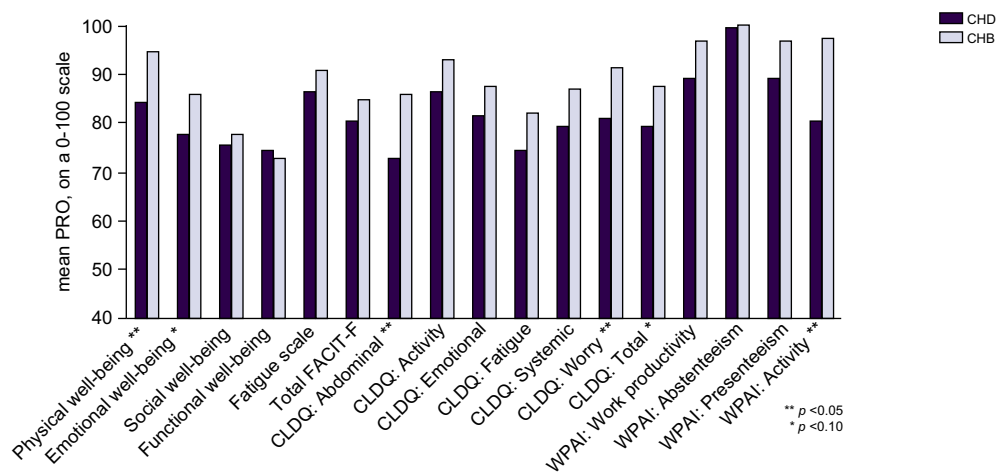


Fig. 1. Patient-reported outcomes comparing patients with chronic hepatitis D and chronic hepatitis B from a baseline characteristic matched cohort. All parameters were normalised to a scale of 0–100 for a comprehensible comparison. The Student *t* test and Mann-Whitney *U* test were used for parametric and non-parametric categories, respectively. Values of *p* ≤ 0.05 were considered statistically significant. CHB, chronic hepatitis B; CHD, chronic hepatitis D; CLDQ, Chronic Liver Disease Questionnaire; EWB, emotional well-being; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FS, fatigue scale; FWB, functional well-being; PWB, physical well-being; SWB, social well-being; WPAI, Work Productivity Activity Impairment.

The total FACIT-F score on a scale of 0–160 was 131.4 ± 24.5 in patients with CHD and 128.1 ± 25.2 in patients with CHB (*p* = 0.3285). A better functional well-being score was observed in CHD than in CHB (*p* = 0.0281), with no other significant differences in other domains. The results of the WPAI questionnaire showed that patients with CHD had a higher activity impairment score than patients with CHB (*p* = 0.0029). No other differences were observed in other domains (Table S1).

In multivariate analysis, a generalised linear regression model showed that having CHD as opposed to having CHB, was an independent predictor of a worse worry score (beta = -0.34, *p* = 0.0394) and high activity impairment (beta = +0.13, *p* = 0.0010).

Regarding educational levels in all patients, results showed that patients with secondary or higher education (*N* = 57) had better HRQoL than those with none or primary educational level (*N* = 67) in the abdominal, activity, emotional, fatigue, and systemic domains of the CLDQ, as well as in all domains of the FACIT-F.

Regarding employment status, those with full time or part time jobs (*N* = 80) had significantly higher HRQoL scores than those who were unemployed (*N* = 45) in the physical, social, and fatigue domains of the CLDQ, as well as the abdominal, activity, fatigue, systemic, and worry domains of FACIT-F. When studying the housewife (*N* = 18) vs. non-housewife (*N* = 107) population, data revealed better HRQoL in the housewife group (physical, emotional, and fatigue domains of CLDQ, and abdominal, activity, fatigue, systemic, and worry domains of FACIT-F).

Very similar reproducible results were observed when studying the CHD group and CHB group separately.

Patient-reported outcomes in CHD- and CHB-matched patients

Of all patients with CHD who were included, *n* = 35 had a matched control with CHB. In this analysis again the majority of patients with CHD were male, Caucasian, and employed. Neither ALT, AST, and platelet levels nor APRI and FIB-4 scores were

significantly different between cases and controls (all *p* > 0.05; Table 2).

The mean CLDQ total score was 5.76 ± 1.06 in those patients with CHD and 6.27 ± 0.53 in controls with CHB (*p* = 0.07). Patients with CHD had a significantly worse worry score (*p* = 0.0021) and more abdominal symptoms (*p* = 0.0364) than patients with CHB. There were no other differences in other CLDQ domains.

The total FACIT-F score on a scale of 0–160 was 129.4 ± 24.5 in patients with CHD and 136.8 ± 14.2 in patients with CHB (*p* = 0.4416). Poorer physical well-being (*p* = 0.0036) and emotional well-being (*p* = 0.0541) was observed in CHD than in CHB, with no other significant differences in other domains. The results of the WPAI questionnaire showed that patients with CHD had a higher activity impairment score than patients with CHB (*p* = 0.0008). No other differences were observed in other domains (Fig. 1 and Table S2).

Patient-reported outcomes in relation to the presence of hepatitis D viraemia

Within the CHD group (*N* = 43), PROs were analysed in relation to the presence of hepatitis D viraemia. Twenty-six (60%) patients had persistently detectable HDV-RNA (active infection) and 17 (40%) patients had undetectable HDV-RNA. There were no differences in the overall scores for the 3 questionnaires relative to those with persistently undetectable HDV-RNA (all *p* > 0.10).

PROs were also evaluated in relation to the HDV viraemia levels. Patients with high levels (≥ 2,000 IU/ml) of baseline HDV-RNA (*N* = 19, 44%) proved to have higher activity impairment on the WPAI questionnaire than those with low HDV-RNA levels (< 2,000 IU/ml) (*p* = 0.024).

Patient-reported outcomes in relation to liver cirrhosis

No patients with CHB presented liver cirrhosis at baseline or at 1 year of follow-up. Patients with CHD with and without liver cirrhosis at baseline were compared. Results showed that patients with CHD and liver cirrhosis (*N* = 14) had a worse CLDQ

systemic score than those without liver cirrhosis (N = 29), $p = 0.0442$.

Discussion

This is, to our knowledge, the first study reporting HRQoL through the evaluation of CLDQ, FACIT-F, and WPAI questionnaires in patients with CHD. Overall, the study shows that patients with CHD have higher HRQoL impairments than patients with CHB, especially in the worry, emotional, physical, and activity impairment domains.

Accurate HRQoL assessment can provide valuable information for clinical practice and designing public health policies.^{36,37} PROs evaluated using CLDQ, FACIT-F, and WPAI tools have been widely validated for CHC and CHB. However, there are no data for CHD. It is well known that the individual and subjective nature of a patient's perception, together with social and cultural influences, make HRQoL difficult to measure.^{38–40}

The CLDQ has been designed as a liver-disease-specific questionnaire, that is reliable, reproducible, easy to use, and has been well-validated in patients with CHC or CHB^{16,41} and is anchored by a 2-week recall period.

Fatigue is a common symptom in chronic liver disease, and various questionnaires can be used to evaluate it. FACIT-F has been widely used in hepatitis C patients and it is easy to perform.³⁰ In studies comparing PROs related to fatigue in patients with CHB or CHC and in the general population, poorer scores were found in patients with chronic viral disease, with no differences between the 2 conditions.⁴² In our study, there was a tendency for patients with CHD to have a poorer well-being score, which has also been shown in studies with CHB.

Overall, PRO scores are reported to be poorer in patients with CHC than with CHB, which could be explained by a weaker systemic and differentiated inflammatory impact of HBV infection.^{43,44} Similarities in the systemic effects of HDV and HBV chronic infection could justify the smaller differences in HRQoL found here.

An intriguing finding of our study is that the presence of hepatitis D viraemia did not impact in PROs as has been seen in

patients with CHB, where suppression of viral replication has been associated with better PROs scores. Only among patients with HDV-RNA levels >2,000 IU/ml, a significant impairment of activity has been observed in relation with those with low or undetectable HDV-RNA levels. In our patients with CHD, HBV-DNA levels were very low or suppressed because of the inhibiting effect of HDV over HBV and/or NAs treatment, as has been previously reported in several studies.²³ In CHC patients, an improvement has been described in HRQoL after DAA treatment and subsequent elimination of hepatitis C.^{45,46} The lack of an effective and safe curative treatment for either CHD or CHB could also contribute to the absence of differences between the 2 groups.

Significant differences between educational level, employment status, and housewife population results are in line with those observed in other general population studies^{47–49} and even in chronic disease populations.⁵⁰ No associations were observed in CHD or CHB groups separately.

Our study has some limitations. First, the number of patients with CHD included is small owing to the limitations in the inclusion criteria, no comorbidities, no previous therapy with interferon, and compensated liver disease. Second, all patients were enrolled in an academic centre with an active liver transplant program that probably had patients with more severe hepatitis D than those observed in other centres.

New therapies for hepatitis D infection are emerging, such as lonafarnib, REP2139, other drugs used for hepatitis B, and combinations of drugs with different mechanisms of action.⁵¹ These drugs have the potential effect to eliminate hepatitis D with different safety profiles. Therefore, it will be fundamental to monitor PROs during the course of these new therapies.

In conclusion, PROs estimating HRQoL in patients with CHD showed to be more impaired than those observed in CHB. HDV viraemia does not seem to impact on PROs unless the levels of HDV-RNA are high. This first results in HRQoL in patients with CHD need to be validated in a larger cohort of patients.

Abbreviations

ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CHD, chronic hepatitis D; CLDQ, Chronic Liver Disease Questionnaire; DAA, direct-acting antivirals; EMA, European medicines agency; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FIB-4, Fibrosis-4; HRQoL, health-related quality of life; IFN, interferon; LLOD, lower limit of detection; LLOQ, lower limit of quantification; NAs, nucleos(t)ide analogues; pegIFN, pegylated interferon; PROs, patient-reported outcomes; WPAI, Work Productivity and Activity Impairment.

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Conflicts of interest

MB and RE have served as a speaker and advisory board member for Gilead, Roche, and Arbutus. MRB has served as a speaker for AbbVie and Gilead. ZY has received research funds from Intercept, Merck, BMS, and Siemens, and has served as consultant for Gilead, Terns, Viking, Intercept, Merck, AbbVie, Novartis, BMS, Shionogi, and Siemens.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Guarantor of the article and responsibility for the integrity of the work as a whole, from inception to published article: MB. Designed the study: MB, FN, ZY. Collected the clinical and laboratory data: LR, AP. Carried out the analysis and interpretation of data: MS, MRB. Drafted the manuscript: LR, AP. Reviewed the manuscript: MB, MRB, ZY, FN. Approved the final version of the article: all authors

Data availability statement

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

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2021.100280>.

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