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HepaDisk – A new quality of life questionnaire for HCV patients

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ABSTRACT

Background: Since most patients with hepatitis C virus (HCV) infection now receive treatment irrespective of liver disease severity, special attention to patient quality of life (QoL), including psycho-social aspects, is required. No QoL questionnaire is specific for patients with HCV.
Aims: To develop and validate a short Italian questionnaire (HepaDisk) assessing the QoL of patients affected by HCV with intuitive graphic results that is understandable by patients and physicians.
Methods: A questionnaire, drafted by a steering committee, underwent a Delphi survey. A multicenter, observational study was conducted to validate the developed HepaDisk versus other tools (CLDQ-I, SF-36, WPAI:HCV), and to evaluate its correlation with disease severity in Italian patients with HCV.
Results: The 10-item questionnaire was validated in 214 patients. HepaDisk showed a high correlation with CLDQ overall score and WPAI:HCV activity impairment (Spearman's rank correlation: 0.651 and 0.595, respectively) and a lower correlation with SF-36. Strong internal consistency (Cronbach coefficient: 0.912), good test–retest reliability (Pearson's correlation coefficient: 0.789; 95% CI, 0.714–0.865), and responsiveness to changes among improved patients were demonstrated.
Conclusion: HepaDisk is a reliable and user-friendly tool that can monitor disease impact on patient QoL over time, providing a visual representation easily understandable by both patients and physicians.

1. Introduction

In the past few years, the pivotal change brought about by the introduction of direct-acting antiviral agents (DAAs) into the therapeutic armamentarium for the treatment of hepatitis C virus (HCV) infection has greatly contributed to increased awareness of

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the medical community toward hepatitis C. DAAs have markedly enlarged the number of possible beneficiaries of curative treatments to include patients previously rarely considered, such as the elderly and those with minimal liver disease. Therefore, the interest for the psycho-social aspects of chronic hepatitis C and associated conditions is mounting. Indeed, hepatitis C, now considered a disease that affects the whole body and not just the liver, is associated with marked psychiatric morbidity and social impairment, characterized by anxiety, depression, social withdrawal, significant reduction of the quality of life (QoL), feelings of stigmatization, and loss of productivity [1–8].

To date, several validated instruments to assess the clinical severity of hepatitis C are available, while only a few specific instruments assessing the impact on QoL and working capability of liver disease have been developed and validated [9–14]. Moreover, the impact of HCV infection on patient QoL is rarely, if ever, assessed outside specialized centers [15,16]. It has been suggested that routine assessment of QoL for patients with HCV would lead to improved patient satisfaction and clinical outcomes [16].

One of the reasons of the poor assessment of QoL in clinical practice may be the lack of visually intuitive instruments that are quick and easy to administer [16]. Therefore, a questionnaire that allows a quick assessment of the impact of the disease, and at the same time, an intuitive graphic visualization of the outcome, might be useful in daily practice. In particular, making the results of the test available to the patient for discussion during the meeting with the physician is likely to increase the patient's perceived control of the disease.

Therefore, we aimed to develop and validate the first Italian visual tool (HepaDisk) for the assessment of QoL in patients with HCV infection. This tool is characterized by both the comprehensiveness of a short questionnaire and the intuitiveness of a graphic representation of the outcome, easily understood by both patients and physicians.

2. Materials and methods

2.1. Delphi method

A steering committee drafted a set of dimensions and related questions (items) in the Italian language, with the aim of evaluating the impact of HCV infection on the QoL of patients. This preliminary HepaDisk version underwent a Delphi [17,18] survey conducted via e-mail and managed by a private market research company (ThinkTank, Milan, Italy). A national panel of experts was provided with the questionnaire by e-mail, together with a detailed instruction sheet and the project's most relevant literature. In two sequential anonymous rounds, participants were asked to indicate their level of agreement for each item on a 10-point numerical rating scale (ranging from 0 = no importance/disagreement to 9 = utmost importance/agreement) on the appropriateness of the item. After each round, the steering committee reviewed the panelists' level of agreement and comments and modified the set of dimensions/items accordingly. Consensus for inclusion of an item in the HepaDisk was defined a priori as ≥70% of panelists rating an item 5 or above.

A steering committee member was defined as a key opinion leader in HCV and an expert in hepatic disease QoL assessment tools. An expert/panelist was defined as a physician with relevant clinical expertise in HCV and patient management, specialized in gastroenterology, internal medicine, or infectious disease. The distribution of the Italian hepatology centers was geographically balanced to reflect the national epidemiology of the disease [19,20].

2.2. Validation study

A multicenter, observational study was conducted with the primary objective of validating the developed HepaDisk questionnaire with respect to other already validated tools (Chronic Liver Disease Questionnaire [CLDQ], 36-item Short Form Health Survey [SF-36], and Work Productivity and Activity Impairment – Hepatitis C Virus [WPAI:HCV]) and to evaluate its correlation with disease severity, assessed through Metavir score, in Italian patients with HCV. Secondary objectives were to assess patient perception/satisfaction of the use of the new instrument, to examine the influence of the use of the new instrument on the patient–physician relationship, and to evaluate the impact of HCV on working ability using the WPAI:HCV.

2.3. Centers and subjects

The study was conducted in Italian centers treating patients with HCV, with at least 10 subjects with HCV infection followed by the outpatient clinic per month. Inclusion criteria were: male and female patients aged ≥18 years old; affected by HCV of any grade of severity and either treated or not with any antiviral drug, and able to understand and complete study-related questionnaires. Patients currently or previously addicted to drugs, with relevant psychiatric comorbidities or taking part in a clinical trial, were excluded from the study. Each subject attended three visits, which were carried out in accordance with the normal clinical practice at each center: visit (V) 2 occurred between 2 to 7 days after V1, and V3 took place 14 weeks (no therapy or 3-month therapy) or 26 weeks (6-month therapy) after V2.

2.4. Questionnaires

The HepaDisk questionnaire is composed of 10 questions. Patients were to answer each question, together with the physician, by indicating their perception of HCV burden on a visual analogue scale (VAS) ranging from 0 (absolutely not) to 10 (definitely yes). The total score is the sum of the single VAS (0 = no impact of the disease on QoL; 100 = maximum impact of disease on QoL). It was provided at all visits on a tablet device, developed in accordance with the US FDA PRO Guidance for Industry [21]. The device did not permit unanswered questions. The other questionnaires were provided at V1 and V3 as hard copy.

The CLDQ is a specific health-related QoL assessment designed for patients with liver disease [12]. In this study, we used the validated Italian version of the questionnaire (CLDQ-I) [15], which includes 28 items scored from 1 (never) to 6 (always), where 6 denotes the worst possible function. It includes a second part that inquires about changes from the last visit in six areas: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry. The total score is the sum of the items' score (28 = minimal impact on QoL; 168 = maximum impact on QoL). No more that 20% of missing data were allowed. In cases of <20%, the missing values were replaced with the mean of the available items.

The SF-36v2 is a multi-purpose, 36-item generic health survey. The 36 items are divided into eight scales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The scales are aggregated into two summary scores, a mental component summary and a physical component summary. All but one of the items (health transition) are used to score the scales [22]. SF-36 is scored on the Quality Metric Incorporated Web site (http://www.QualityMetric.com/) [23]; higher scores indicate better health. In this study, we used the Italian translation of the survey (SF-36v2 standard Italy [Italian] version 2.0, 3/03). Missing values were not replaced; in case of a missing question, the total score was set to missing.

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The WPAI:HCV is a 6-item questionnaire on the effect of HCV on the ability to work and perform regular activities. Questions explore the effect of HCV on patients' ability to work and perform regular activities: employment status, hours missed from work due to HCV, hours missed from work due to other reasons, hours actually worked, degree HCV affected productivity while working (score from 0 to 10), and degree HCV affected regular activities (score from 0 to 10) [24]. WPAI outcomes are expressed as impairment percentages (response scores multiplied by 100), with higher numbers indicating greater impairment and less productivity, as follows: percentage of work time missed due to health; percentage of impairment while working due to health; percentage of overall work impairment due to health; and percentage of activity impairment due to health [25]. The Italian translation used in this study (Italian for Italy – WPAI:Hepatitis C V2.3 – 24/MAR/2014) was created by RWS Life Sciences [26]. Missing values were handled as per copyright holder instructions [27].

The Subject Satisfaction Questionnaire was created by the study team. The questions ask patients about their perception of the severity of their disease; if the physician showed interest in them as a person, if answering the HepaDisk questionnaire helped the physician to understand how the patient experiences the disease, and if the HepaDisk questionnaire has provided the physician with a satisfactory overall understanding of the problems the patient experiences because of the disease. All questions have five responses, ranging from "not at all" to "very much so."

2.5. Sample size

The sample size was determined according to feasibility criteria [28]. According to these criteria, a total of 10 subjects per item of the questionnaire was needed. The HepaDisk questionnaire consists of 10 items; hence, a minimum sample size of 100 subjects was required. Due to the expected high rate (35%) of missing data or failure to complete paper questionnaires and drop-out rate (based on previous experience from PSOdisk questionnaire validation [29]) and in order to reach statistical significance in case it was possible to perform the analyses on 150 patients staged F0–F2 and 150 staged F3–F4, the sample size was increased to 300 subjects.

2.6. Psychometric evaluation

The evaluation was performed using the data collected at three different visits: V1, V2 and V3. The face and content validity was assessed using the Delphi method as described above. The construct validity was evaluated clinically and psychometrically at V1. First, differences in scores in groups differing in severity of HCV infection and in QoL were analyzed using the Spearman's rank correlation, hypothesizing that patients with a higher level of disease severity and a worse QoL would also have a higher HepaDisk score. Secondly, an exploratory factor analysis was performed to identify the factor structure underlying the HepaDisk items. Under the hypothesis that the underlying factors are correlated, mainly in physical, mental, and social subdomains, principal axes factor analysis, followed by an oblique rotation, was applied. The number of factors was determined by retaining only those factors with an eigenvalue >1 after factor rotation. The internal consistency reliability was evaluated at V1 using the Cronbach's coefficient alpha, a parameter calculated from the pairwise correlations between the 10 items of the HepaDisk questionnaire. Internal consistency ranges between zero and one: 0.6–0.7 indicates acceptable reliability and ≥0.8 indicates good reliability.

For test–retest reliability assessment, the same respondents completed the questionnaire twice at V1 and V2. The correlation between the two sets of responses was provided in terms of Pearson's correlation coefficient. The less scattered the results, the greater the test–retest reliability of the study instrument.

The responsiveness to change was tested at V3 using the paired *t* test to compare the changes in scores in patients whose clinical condition had overall improved, stayed the same, or worsened since V1. Clinical improvement was assessed through viral load and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) changes.

3. Results

3.1. Delphi method

The steering committee that drafted the initial set of dimensions and items of the HepaDisk was made up of four clinical experts, with the aid of a representative of the Italian patient association for hepatitis C (EpaC); at the end of round 2, the steering committee (four clinical experts) developed the final HepaDisk version.

Of the 100 HCV experts selected, 77 agreed to participate; 69 experts (median number of new patients/year: 90; median years of clinical experience in HCV: 20 years, 95% CI, 3–40 years) returned the first round of the survey and 55 completed the second round. The geographical distribution of the centers involved in round 1 and 2 was 14 and 11 in northern Italy, 13 and 11 in central Italy, and 42 and 33 in southern Italy, respectively.

The Delphi process was conducted between November 2014 and May 2015, with round 1 and 2 data collected over 2 months and 3 weeks, respectively. After each round, ThinkTank provided a report to the steering committee with graphs summarizing the results for each item as well as the comments. The steering committee reviewed the results in a 1-day meeting and modified the questionnaire accordingly.

The flowchart of the evolving of consensus over the rounds is detailed in Fig. 1 and the description of the results is presented in the supplementary materials. The developed HepaDisk is a 10-item questionnaire (Fig. 2).

3.2. Validation study

The study protocol was approved by each local ethics committee. All patients signed the informed consent form and the authorization to the treatment of personal data prior to any study-related activity. Of the 301 patients enrolled in 23 centers, 265 (88%) were eligible for the study (eligible population) and attended V1 and V2; 263 patients attended V3. Two patients did not complete the study (1 lost to follow-up; 1 withdrawal). The per-protocol population (all visits fully completed) consisted of 214 patients enrolled in 22 centers. The baseline demographics and clinical characteristics of the eligible and per-protocol population are described in Table 1.

The per-protocol population perception of HCV severity, measured through the Subject Satisfaction Questionnaire, was severe/very severe (23.8% and 15.0%), fair (38.3% and 40.2%), and mild/very mild (37.9% and 44.4%) at V1 and V3, respectively.

The second part of the CLDQ-I was not used, as it was not needed for the validation of the HepaDisk.

3.3. Psychometric evaluation

The psychometric evaluation and secondary analysis were performed using data from the per-protocol population.

3.3.1. Construct validity

All questionnaires showed no significant correlation with the physician's and Metavir evaluation of HCV severity and a small grade of correlation with the subject's perception of the disease

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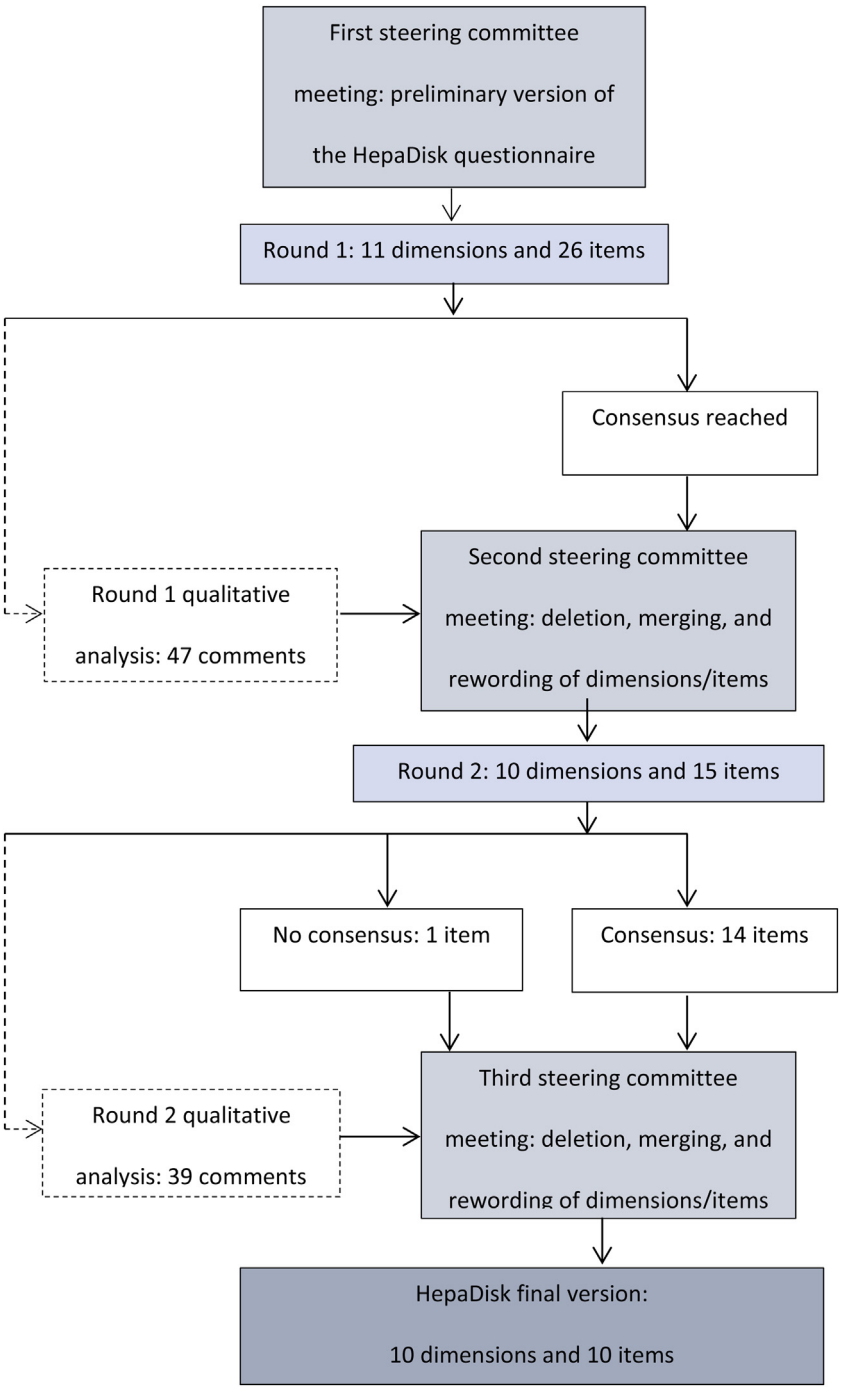

Fig. 1. Stages of the Delphi process and attainment of consensus.

(Table 2), as confirmed by HepaDisk scores stratified by grade of subjects' perception (Fig. 3).

The HepaDisk questionnaire scores showed a moderately high correlation with CLDQ-I overall and WPAI:HCV scores and a lower correlation with SF-36 scores (Table 3).

The factor analysis identified two factors at V1 (the percentage of total variance explained by both factors was >65%), and it was possible to group the items into two domains: one defined by psychological patterns (social life, peace of mind, relationships, sexuality, life habits, and capability to plan the future), and the other by physical ones (health, lack of energy, sleep, and work); each factor was strongly correlated to all its individual items except for work. At V3, only one latent factor was identified that explained around 70% of the total variance, and it was strongly correlated to all of the individual items.

3.3.2. *Internal consistency reliability*

The Cronbach's coefficient alpha was 0.912, indicating very good internal consistency reliability.

3.3.3. *Test–retest reliability*

Good test–retest reliability between V1 (39.2 ± 26.8) and V2 (36.9 ± 26.5) was observed, with a Pearson's correlation coefficient of 0.789 (95% CI, 0.714–0.865).

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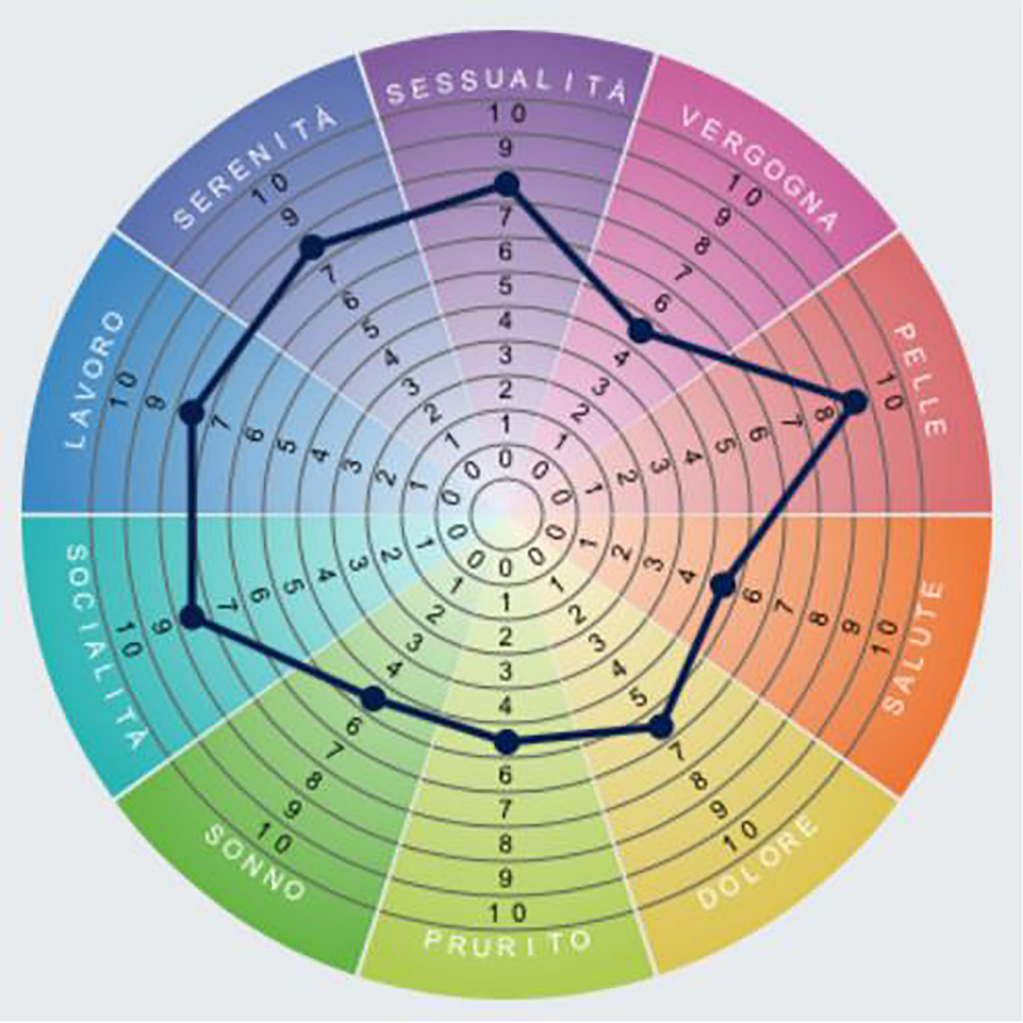

Fig. 2. The Italian HepaDisk questionnaire, with an example of polygons derived from answers to the 10 items.
Health (salute): hepatitis C damages my health status; lack of energy (calo di energia): hepatitis C makes me feel tired during normal daily life; sleep (sonno): hepatitis C damages the quality of my sleep; social life (vita sociale): hepatitis C damages my social life (i.e., convivial events, kind of sport activities, kind of holidays); peace of mind (serenità mentale): hepatitis c prevents me from facing my daily life untroubled; work (lavoro): hepatitis C damages my working life; relationships (vita affettiva): hepatitis C influences my decisions on my relationships; sexuality (vita sessuale): hepatitis C influences my sexuality; life habits (abitudini di vita): hepatitis C damages my life habits (i.e., going to the hairdresser, barber, beautician, dentist, body piercing, tattooing); capability to plan future (progettare il futuro): hepatitis C damages my will to make future plans.

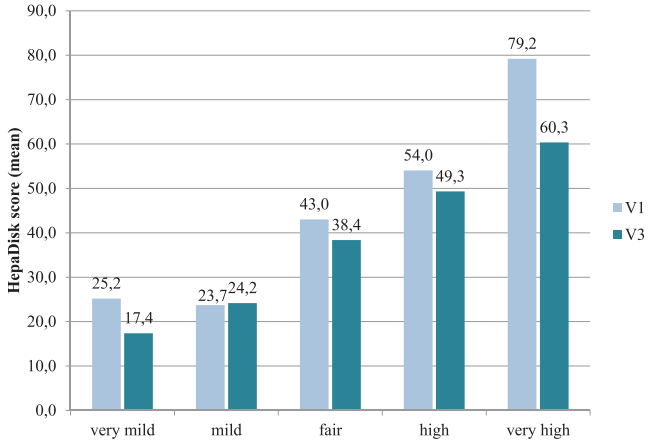

Fig. 3. HepaDisk scores by subject's perception of the severity of the disease.

3.3.4. Responsiveness to change

Among improved patients for viral load decrease (n = 141) at V3, a statistically significant decrease (−9.96 ± 26.77, p < 0.001) was noted on the HepaDisk questionnaire; no statistically significant changes were noted among stable (n = 53, −2.08 ± 21.84, p = 0.49) or worsened patients (n = 20; 2.90 ± 21.70, p = 0.56).

Among improved patients for AST/ALT decrease (n = 125) at V3, a statistically significant decrease (−11.73 ± 25.28, p < 0.001) was noted on the HepaDisk questionnaire; no statistically significant changes were noted among stable (n = 41; −2.68 ± 21.95, p = 0.44) or worsened patients (n = 48; 2.48 ± 26.16, p = 0.52).

3.4. Secondary analysis

Seventy percent to 89% of patients were "Quite a lot" to "Very much so" satisfied with the use of the HepaDisk and considered it important, giving their physician a better understanding of HCV-related concerns.

The mean impact (% ± SD) of HCV on working ability through the WPAI:HCV was 22.8 ± 28.9 for activity impairment, 4.0 ± 9.2 for absenteeism, 19.6 ± 26.3 for presenteeism, and 17.2 ± 22.9 for total working impairment.

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Table 1
Demographics and clinical characteristics at baseline.

		Eligible population(N = 265)		Per-protocol population (n = 214)	
		n	%	n	%
Sex	Male	128	48.3	101	47.2
	Female	137	51.7	113	52.8
Age (years)	Mean ± SD (range)	61.4 ± 12.5 (25–84)		61.7 ± 12.7 (25–84)	
Civil status	Single	31	11.7	25	11.7
	Married or living together	195	73.6	155	72.4
	Separated or divorced	19	7.2	18	8.4
	Widow/widower	20	7.5	16	7.5
Education level	Primary school	61	23.0	43	20.1
	Secondary school	107	40.4	87	40.7
	High school	63	23.8	55	25.7
	University	34	12.8	29	13.5
Smoking habits	Smoker	66	24.9	53	24.8
	Never smoked	148	55.8	115	53.7
	Ex-smoker (>6 months)	51	19.2	46	21.5
Alcohol consumption	Drinker	27	10.2	25	11.7
	Drinker mean ± SD (range) alcohol consume (units/day)	3.7 ± 9.9 (1–50)		4.0 ± 10.3 (1–50)	
	Non-drinker	186	70.2	141	65.9
	Ex-drinker (>6 months)	52	19.6	48	22.4
BMI, kg/m^2	Mean ± SD (range)	25.4 ± 4.0 (17–39)		25.3 ± 3.9 (17–39)	
GT at diagnosis	GT1a	32	12.1	25	11.7
	GT1b	144	54.3	114	53.3
	GT2	57	21.5	49	22.9
	GT3	16	6.0	14	6.5
	GT4	15	5.7	11	5.1
	GT5	1	0.4	1	0.5
Metavir at diagnosis	F0	70	26.4	58	27.1
	F1	68	25.7	53	24.8
	F2	43	16.2	36	16.8
	F3	47	17.7	40	18.7
	F4	37	14.0	27	12.6
	Unknown	185	69.8	156	72.9
Route of transmission	Blood transfusion	43	16.2	29	13.6
	Blood contact	16	6.0	9	4.2
	Sexual	13	4.9	12	5.6
	Other	7	2.6	7	3.3
	Mother to child transmission	1	0.4	1	0.5
Liver transplantation		2	0.7	2	0.9
Cirrhosis		49	18.5	36	16.8
Decompensation		0	0.0	0	0.0

BMI, body mass index; GT, genotype; SD, standard deviation.

Table 2
Correlation between questionnaires and severity of disease evaluated by physician, Metavir score and subject.

	Physician evaluation		Metavir		Subject perception	
	Spearman's rank correlation	P value	Spearman's rank correlation	P value	Spearman's rank correlation	P value
HepaDisk	−0.011	0.878	0.004	0.949	0.48	<0.001
SF-36: PCS	−0.167	0.015	0.079	0.252	−0.403	<0.001
SF-36: MCS	0.103	0.132	−0.017	0.807	−0.327	<0.001
CLDQ: overall score	−0.013	0.847	−0.041	0.547	0.425	<0.001
CLDQ: abdominal symptoms	−0.062	0.365	−0.119	0.084	0.3	<0.001
CLDQ: fatigue	0.013	0,855	−0.056	0.416	0.397	<0.001
CLDQ: systemic symptoms	0.037	0,588	−0.053	0.438	0.357	<0.001
CLDQ: activity	0.09	0,191	0.029	0.679	0.369	<0.001
CLDQ: emotional function	−0.106	0.121	−0.017	0.798	0.343	<0.001
CLDQ: worry	0.048	0.485	0.04	0.561	0.384	<0.001
WPAI:HCV: activity impairment	0.002	0.976	−0.044	0.528	0.462	<0.001

CLDQ, Chronic Liver Disease Questionnaire; MCS, mental component summary; PCS, physical component summary; SF-36, 36-item Short Form Health Survey; WPAI:HCV, Work Productivity and Activity Impairment: Hepatitis C Virus.

4. Discussion

4.1. Delphi method

The 10-item questionnaire that was developed is intended to be filled out by the patient with the physician during a routine visit, fostering a better communication between them, which may positively influence treatment adherence. The answers to the questions are represented graphically on a colored disk as a polygon (Fig. 2). When the burden of the disease decreases, the area of the polygon shrinks, providing both the physician and the patient with an immediate and intuitive representation of the progress achieved. It is administered on electronic devices, offering physicians a fast

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Table 3
Correlation between questionnaire scores.

Correlation of HepaDisk with:	Spearman's rank correlation	P value
CLDQ: overall score	0.651	<0.001
CLDQ: abdominal symptoms	0.509	<0.001
CLDQ: fatigue	0.571	<0.001
CLDQ: systemic symptoms	0.54	<0.001
CLDQ: activity	0.535	<0.001
CLDQ: emotional function	0.555	<0.001
CLDQ: worry	0.562	<0.001
SF-36: PCS	−0.432	<0.001
SF-36: MCS	−0.552	<0.001
WPAI:HCV: activity impairment	0.595	<0.001

CLDQ, Chronic Liver Disease Questionnaire; MCS, mental component summary; PCS, physical component summary; SF-36, 36-item Short Form Health Survey; WPAI:HCV, Work Productivity and Activity Impairment – Hepatitis C Virus.

and easy-to-read response for their routine clinical practice or for clinical studies.

A possible limitation of the Delphi process is the panel of experts involved potentially not representing the view of all Italian physicians treating patients with HCV infection. To minimize this limitation, we included experts in gastroenterology, internal medicine, and infectious disease and balanced the geographical distribution of the centers to reflect the national epidemiology of the disease.

4.2. Validation study

The grade of correlation of the severity of disease versus questionnaire scores recorded for the HepaDisk scores was substantially similar to the other questionnaires. The grade of correlation of the HepaDisk scores versus other questionnaires was moderately high versus CLDQ-I (overall score) and WPAI:HCV (activity impairment) and lower versus SF-36; this could be imputable to the different nature of the two questionnaires, as HepaDisk investigates the status of the patients with a specific pathology (HCV), while the SF-36 aims to evaluate the general status of health of the patients. This evidence supports the clinical value that the HepaDisk can bring to clinical practice. The factor analysis showed that HepaDisk is composed of a single domain without any subdomain, thus allowing calculating the total score as the sum of the scores of each question. The HepaDisk also demonstrated strong internal consistency reliability, the measure of how well the items on a test measure the same construct or idea. The good test–retest reliability results highlighted the high reproducibility of our tool in a short time interval, when the clinical conditions are expected to be the same and therefore the QoL should be almost the same. Finally, HepaDisk detected a statistically significant difference when the patient's HCV severity improved, similar to the CLDQ-I and SF-36 instruments, as assessed in a 14/26 weeks' time frame (V3). There was a statistically significant decrease in scores ($p < 0.001$) among improved patients ($n = 141$); there was no statistically significant change among stable ($n = 53$; $p = 0.49$) or worsened patients ($n = 20$; $p = 0.56$).

A possible limit of this study could be the use of "non-disease-specific" QoL tools, CLDQ-I and SF-36, as comparison questionnaires; further analysis comparing HepaDisk scores versus other HCV-specific QoL tools might provide a deeper understanding of the new questionnaire efficacy. Another limitation of our study may be the questionnaire's development based on and targeted for the Italian population and its local language. In order to spread its use internationally, HepaDisk should be translated and its psychometric properties tested in other populations accordingly.

In conclusion, the development and validation of the HepaDisk questionnaire provides patients and clinicians with a reliable and user-friendly tool that should help monitor the impact of HCV on different aspects of a patient's QoL over time by means of an intuitive graphic representation. Moreover, the HepaDisk might allow for the correlation of treatment outcomes and QoL, potentially increasing the control of disease perceived by patients.

Conflicts of interest

Giuliana Gualberti and Valeria Saragaglia are employees of AbbVie and may own AbbVie stocks/options. Fabio Buelli was an AbbVie employee and may own stocks/options.

S Fagiuoli declares speaker bureaus and advisory boards for BMS, MSD, AbbVie, Gilead, Novartis, Grifols, Kedrion, and Bayer.

N Caporaso declares research grants, lecturing fees, advisory boards, and scientific consultancy for AbbVie, BMS, Gilead Science, Janssen, and MSD.

F Morisco declares advisory boards and congress participation for AbbVie, Gilead, Bristol and MSD.

L Chessa declares participation in advisory boards for AbbVie and speaker fees for AbbVie and Gilead.

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M Pirisi declares lecture fees from Gilead, Bayer, AbbVie, and Alfasigma and participation in advisory boards for Bayer and MSD.

FP Russo declares speaker bureaus and advisory boards for BMS, MSD, AbbVie, Gilead, Biotest, grants from Abbvie and BMS.

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J Vecchiet received grants from AbbVie.

M Vinci received grants from Abbvie, declares participation in advisory boards for AbbVie, speaker fees for Abbvie and Gilead.

G Taliani declares speaking and teaching fees from AbbVie, BMS, Gilead, MSD Italia.

P Toniutto declares speaker bureaus and advisory boards for BMS, MSD, AbbVie, Gilead, Novartis, Kedrion.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.12.009.

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