

## Quality of life in Brazilian patients with treated or untreated chronic hepatitis C

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### ABSTRACT

**Introduction:** Multiple factors negatively affect the quality of life of patients infected with hepatitis C virus. This study aims to evaluate the effect of pharmacological treatment on the quality of life of these individuals. **Methods:** This is a cross-sectional study conducted in two Southern Brazilian centers that used two instruments (a generic and a specific one) for measuring the quality of life in patients with chronic hepatitis C: the Short Form-36 (SF-36); and the Chronic Liver Disease Questionnaire (CLDQ) for liver disease. We included patients from two centers without any treatment (control group), or receiving medication (peginterferon + ribavirin ± telaprevir or boceprevir, i.e., respectively, dual, and triple therapies). **Results:** One hundred and forty-seven patients were included. Patients under treatment (n = 86) had a lower score in 7 of the 8 SF-36 domains, with statistical significance (p<0.05) only for the emotional function domain. Patients who were not treated (n = 58) had higher scores in 4 of the 6 (p<0.05) CLDQ domains. A comparison of patients, receiving dual or triple therapies for both questionnaires, was only significant in the Vitality domain from CLDQ. **Conclusions:** Treatment can affect the subjective perception of patients regarding quality of life. Due to the complexity of the disease, each patient must be evaluated in multiple dimensions. Thus, the results may be useful for understanding the patient's perceptions during treatment, and it can also serve as a reference for care instructions.

**KEYWORDS:** Quality of life. Hepatitis C treatment. SF-36. CLDQ.

### INTRODUCTION

Due to its high morbidity rate, chronic hepatitis C currently constitutes a major public health problem. Hepatitis C is considered the most common cause of liver transplantation, with a mortality rate of 399,000 deaths per year. Currently, 71 million people are chronically infected with the hepatitis C virus (HCV), and are at risk for developing cirrhosis or hepatocarcinoma (HCC)<sup>1</sup>. Hepatitis C is not only restricted to the liver; it may also be considered a mental, psychological, family, and social disease because several factors negatively affect the patients' quality of life. Adverse reactions to pharmacological treatment is also a burden for the patient, and along with the social stigmatization, may trigger serious social and familial isolation<sup>2-6</sup>.

For many years, the treatment of chronic hepatitis C was based on the use of interferon, which could be used in combination with ribavirin and/or one of the first direct-acting antivirals (DAA), i.e., boceprevir and telaprevir. The combination of these drugs, in dual or triple therapies, made possible to increase the sustained virological response (SVR), defined as undetectable HCV RNA

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after completion of antiviral therapy, compared to previous therapies. However, these treatments can be problematic due to the high incidence of adverse events, which can lead to treatment discontinuation, and still have limited efficacy, especially compared to a second generation of DAA that has been developed in recent years, and can be combined in therapies without IFN (which are called interferon-free therapies).

The suffering caused by a disease is not limited only by pain or other discomforts, but also by the negative effects on patients' daily lives and their ability to work and develop social relationships. Thus, studies related to quality of life increase the knowledge on the impact of the disease on daily activities, help in the identification of individual problems for each disease, and in the evaluation of treatments and patient adherence, as well as in obtaining essential information to allow the comparison of different treatments<sup>7-10</sup>.

Thus, in order to capture the patients' perspectives during individual and collective health status assessments, quality of life questionnaires are commonly used. These can be general, specific, or modular<sup>11,12</sup>. The generic questionnaires (e.g., Short Form 36 - SF-36) cover an overview of the psychological and social status and also the physical and occupational functions, being used to evaluate a variety of health states and a wide range of diseases<sup>13,14</sup>. Specific questionnaires are applied to specific populations with particular diseases or treatment consequences, such as hepatitis C (e.g., Chronic Liver Disease Questionnaire - CLDQ). Finally, modular questionnaires involve a compound of both, generic and specific issues<sup>15-17</sup>.

In recent years, studies about the evaluation of the quality of life, especially in chronic diseases, have occurred more frequently and attracted the attention of both researchers and political managers. Thus, the present study aimed to evaluate the effect of antiviral treatment on the quality of life of patients with CHC through SF-36 and CLDQ questionnaires.

## METHODS

### Study design

This is a cross-sectional study that was conducted from April 2014 to March 2015. Questionnaires were used to interview patients with CHC, who were under pharmacological treatment or not (control group), in two major medical care centers in the city of Curitiba, State of Paraná (the Clinical Hospital from *Universidade Federal do Paraná* [HC-UFPR] and the Guidance and Counseling Center of the City Health Department [COA-SMS]).

### Study population and data collection

The study included patients with CHC, regardless of gender, who were above 18 years old. Patients were invited to participate in the study while awaiting routine medical consultation. As many patients as possible were interviewed from each center, and the number of patients that refused to participate was inexpressive. Those with a psychiatric diagnosis, women that were pregnant, and patients with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) coinfections, were excluded from the study.

Patients from the HC-UFPR and COA-SMS were invited to participate and answer the questionnaires after signing the informed consent form. The Excel 2013 software was used to assist in the collection and tabulation of collected data.

### Measurement instruments

The researchers applied the SF-36 and the CLDQ questionnaires to assess the patients' reported outcomes (PROs). The final structure of the SF-36 was the one developed by Ware and Sherbourne in 1992<sup>18</sup> and adapted for the Brazilian population by Ciconelli *et al.* in 1999<sup>19</sup>, while the CLDQ was developed by Younossi *et al.*<sup>20</sup> in 1999 and adapted for the Brazilian population by Mucci *et al.*<sup>21</sup> in 2010.

The SF-36 consists of items (questions), scales (for each quality of life domain), and summary measures (physical and mental components). Altogether, there are 36 items divided into 8 domains<sup>22,23</sup>. Although it is not considered a specific domain, the sub-range of health transition intends to quantify the change in a patient's overall health. The SF-36 domains are designated as follows: Physical Health (RL), Physical Functioning (PF), Pain (P) General Health (GH), Vitality (V), Social Functioning (SF), Emotional Well-Being (EW), and Mental Health (MH)<sup>24,25</sup>. Each scale is compounded by 2-10 items. These scales may be summarized through the two summary measures, the physical components (PCom = PF + RL + P + GH) and mental components (MCom = EW + V + SF + MH). Results are expressed as a score ranging from 0 to 100 for each of the eight scales, with higher scores indicating a better quality of life, or through the standardized score in the form of T-scores from the 2009 data for the US population (average of 50 and a standard deviation of 10), which has become much easier for the interpretation of results<sup>12,19,26</sup>.

The CLDQ consists of 29 items that are designed to measure the six domains of quality of life, including the abdominal symptoms (AS), fatigue (FA), systemic symptoms (SS), activity (AT), emotional function (EF), and

worry (WO). This questionnaire has two ways of presenting its scores, with one for each individual, and another for the general domains. Both scores range from 1 (worst) to 7 (least severe), wherein higher scores indicate a minimum frequency of symptoms and, consequently, a better quality of life. The overall score is calculated by averaging the six dimensions<sup>20,21,27</sup>.

## Statistical analysis

Data were entered into an electronic spreadsheet in Excel and subsequently transferred and analyzed using the Minitab® 17. The Kolmogorov-Smirnov test was used to verify the distribution of parameters. As data distribution was not normal, non-parametric tests were applied in the comparative analysis.

The Mann-Whitney test was used for overall analysis and for four sub-analyses to verify possible statistical differences regarding four variables: gender (male versus female), marital status (Married/cohabiting versus single/separated/widowed), comorbidities (yes versus no) and addictions (yes versus no). The four sub-analyses were made for the following groups: patients receiving treatment; patients without treatment; patients receiving IFN+RBV (duo therapy) and patients receiving one of the triple therapies. A p-value < 0.05 was considered significant and a  $\alpha = 5\%$  was adopted.

The study was approved by the Ethics Committee on Human Research of both institutions (approval N° 30486914.0.0000.0096 and 30486914.0.3001.0101 respectively for HC-UFPR and COA-SMS), and is in accordance with the Helsinki Declaration of 1975.

## RESULTS

The study included 147 patients (51% were female) with a median of  $53 \pm 10.9$  years. Most individuals had a primary level of education (55.1%), 54.4% were either married or cohabiting, 73.5% did not report any kind of addiction, and the average monthly income of the group was US\$ 475. The majority of the patients (73.5%) had undergone the genotyping test according to their medical records, and of these patients genotype 1 was predominant (67%). Table 1 presents all the sociodemographic data, and patients were divided into two groups: receiving treatment or not receiving treatment.

Among all the patients, 58 (39.5%) were receiving treatment for CHC. Most of them (69%) received dual therapy (IFNpeg associated with Ribavirin) and the remaining patients received dual therapy combined with one of the first generation DAA, i.e., a triple therapy

(IFNpeg/Ribavirin + telaprevir [13.8%] or boceprevir [17.2%]). Only one patient received telaprevir and IFNpeg without ribavirin (Table 1).

Among the 147 included patients, three patients presented SF-36 scales with scores below 50 (PF, V and EW). Patients who were receiving treatment had lower scores on 7 domains, which was statistically significant ( $p < 0.05$ ) only for the EW domain. Regarding the CLDQ score, patients without antiviral treatment presented a significantly higher overall average (5.39 [1.15]). These patients also presented with significantly higher averages ( $p < 0.05$ ) in 4 of the 6 areas of CLDQ (FA, SS, AT, and EF) (Table 2).

Another analysis was performed to compare domains SF-36 and CLDQ between patients receiving RBV/IFNpeg (dual therapy) and triple therapies (BOC or TVR with RBV/IFNpeg) and a significant statistical difference was observed only in Vitality domain from CLDQ ( $p < 0.05$ ).

Four different sub-analyses (Mann-Whitney test) were conducted (i.e., patients receiving treatment; patients without treatment; patients receiving IFN+RBV; and patients receiving one of the triple therapies), to analyze if there were statistical differences considering four variables: gender (male versus female), marital status (Married/cohabiting versus single/separated/widowed), comorbidities (yes versus no) and additions (yes versus no). Full data from these analyses are presented in Table 3.

## DISCUSSION

Viral hepatitis constitutes a major public health problem. Among them, hepatitis C is considered the most common cause of liver transplantation, especially due to a slowly progressive disease and a high rate of chronicity, which makes it potentially fatal compared to the other types of viral hepatitis.

This study evaluated the effects of antiviral treatment on the subjective perception of the quality of life in patients with CHC. The overall analysis of the SF-36 questionnaire showed a statistically significant difference only in the emotional aspect domain, while CLDQ questionnaire had differences in some domains<sup>28</sup>.

Several factors may contribute to the decrease of patients' quality of life in hepatitis C patients, including natural manifestations of the disease such as fatigue, myalgia, nausea, vomiting, abdominal pain, and mental health problems. These symptoms may also be complications of the antiviral therapy. Adverse reactions of some drugs, such as pegylated interferon, ribavirin, and even protease inhibitors like telaprevir (fever, irritability, rash, itching, and diarrhea) are also contributing factors.

**Table 1** - Comparison of the sociodemographic and clinical categorical variables of the study population

	PARAMETER	Total Patients N (147)	Patients with medication N (58)	Patients without medication N (89)	p-value
<b>GENDER</b>	Male	72 (49%)	31 (53.5%)	41 (46%)	0.382
<b>GENOTYPE</b>					0.128
	1 (Unspecified)	21 (14%)	11 (29%)	9 (10%)	
	1a	25 (17%)	14 (24%)	11 (12.3%)	
	1b	26 (17.7%)	14 (24%)	12 (13.4%)	
	1a e 1b	1 (0.7%)	1 (1.7%)	0	
	2	2 (1.4%)	1 (1.7%)	1 (1.1%)	
	3	33 (22.4%)	9 (15.5%)	24 (27%)	
	4	1 (0.7%)	0	1 (1.1%)	
	Not informed	39 (26.5%)	8 (13.8%)	31 (34.8%)	
<b>RACE</b>					0.183
	White	129 (87%)	52 (89.6%)	77 (86.5%)	
	Black	14 (9.5%)	6 (10%)	8 (9%)	
	Brown	4 (2.7%)	0	4 (4.5%)	
<b>MARITAL STATUS</b>					0.244
	Married or cohabiting	80 (54.4%)	35 (60%)	45 (50.5%)	
	Single/separated/ widowed	67 (45.6%)	23 (39%)	44 (49.4%)	
<b>EDUCATIONAL LEVEL</b>					0.127
	Illiterate	1 (0.7%)	1 (1.7%)	0	
	Elementary School	81 (55.1%)	29 (50%)	52 (58.4%)	
	Secondary School	42 (28.6%)	22 (38%)	20 (22.5%)	
	Technical Degree	2 (1.4%)	1 (1.7%)	1 (1.1%)	
	High School	21 (14.3%)	5 (8.2%)	16 (18%)	
<b>COMORBIDITIES</b>					0.807
	Yes	92 (62.6%)	37 (63.7%)	55 (61.8%)	
	No	55 (37.4%)	21 (36%)	34 (38.2%)	
<b>TREATMENT</b>					
	IFNpeg/RBV	40 (27.2%)	40 (69%)	0	
	IFNpeg/TVR	1 (0.7%)	1 (1.7)	0	
	IFNpeg/RBV/TVR	10 (6.8%)	10 (17.2)	0	
	IFNpeg/RBV/BOC	7 (4.7%)	7 (12)	0	
	None	89 (60.5%)	0	89 (100%)	
<b>ADDICTIONS</b>					0.815
	Yes	39 (26.5%)	16 (27.5%)	23 (25.8%)	
	No	108 (73.5%)	42 (72.4%)	66 (74.1%)	
<b>METAVIR</b>					0.142
	F0	2 (1.4%)	0	2 (2.2%)	
	F1	2 (1.4%)	1 (1.7%)	1 (1.1%)	
	F2	8 (5.4%)	6 (10.3%)	2 (2.2%)	
	F3	11 (7.5%)	8 (13.8%)	3 (3.3%)	
	F4	9 (6.1%)	3 (5.1%)	6 (6.7%)	
	Not informed	115 (78.2%)	40 (69%)	75 (84.2%)	

\*significant. IFNpeg= Pegylated Interferon; RBV= Ribavirin; TVR= Telaprevir; BOC= Boceprevir. F0= no fibrosis; F1= mild fibrosis; F2= moderate fibrosis; F3= severe fibrosis; F4= cirrhosis.

The impact of treatment on the patient's perception of quality of life is very useful, as seen in the numerous medications for CHC control that have been developed in recent years. Although triple therapy promotes higher SVR rates than dual therapy, our study did not show considerable differences in the quality of life between the two treatments. This could be due to the fact that peginterferon was still being used, which is related to an elevated number of side effects and a higher number of injections, which are thus

expected to reduce the quality of life in chronic hepatitis C patients<sup>29-31</sup>.

Three second generation DAA are being used in Brazil since 2015 (i.e., sofosbuvir, daclatasvir and simeprevir)<sup>32</sup>. They are oral drugs related to higher efficacy rates and a better safety profile, which may increase the quality of life of these patients and also of work productivity. This could be associated to the fact that oral antiviral treatment is correlated with a higher quality of life, promotes less side

**Table 2** - Comparison of the SF-36 and CLDQ scores between patients with or without current treatment

Domains of SF-36 and CLDQ		Patients receiving treatment (N=86), Mean (SD)	Patients without any treatment (N=58), Mean (SD)	p-value
SF-36	<b>RL</b>	74.10 (±26.94)	68.96 (±26.65)	0.188
	<b>PF</b>	58.15 (±45.19)	46.98 (±43.95)	0.102
	<b>P</b>	60.92 (±31.23)	54.33 (±32.95)	0.243
	<b>GH</b>	67.65 (±25.25)	67.71 (±22.33)	0.838
	<b>V</b>	58.71 (±30.44)	48.44 (±32.07)	0.057
	<b>SF</b>	75.56 (±28.07)	70.26 (±29.88)	0.335
	<b>EW</b>	62.14 (±46.92)	46.78 (±44.92)	0.037*
	<b>MH</b>	63.73 (±27.68)	59.46 (±29.39)	0.433
	<b>PCom</b>	52.63 (±7.72)	53.65 (±7.99)	0.376
	<b>MCom</b>	54.10 (±14.46)	57.51 (±14.84)	0.162
CLDQ	<b>AS</b>	5.45 (1.59)	5.37 (1.76)	0.351
	<b>FA</b>	4.82 (1.78)	3.96 (1.71)	0.004*
	<b>SS</b>	5.44 (1.37)	4.54 (1.38)	0.000*
	<b>AT</b>	5.87 (1.24)	4.82 (1.48)	0.000*
	<b>EF</b>	5.15 (1.40)	4.64 (1.34)	0.010*
	<b>WO</b>	5.59 (1.38)	5.13 (1.71)	0.148
	<b>Overall score</b>	5.39 (1.15)	4.74 (1.01)	0.000*

\*p<0.05; Abbreviations: RL, Role Limitations due to Physical Health; PF, Physical Functioning; P, Pain; GH, General Health; V, Vitality; SF, Social Functioning; EW, Emotional Well-Being; MH, Mental Health; PCom, Physical Component; MCom, Mental Component; AS, Abdominal Symptoms; FA, Fatigue; SS, Systemic Symptoms; AT, Activity; EF, Emotional Function; WO, Worry.

**Table 3** - Results of the Mann-Whitney test relating variables (gender, marital status, comorbidities and addictions) to the fact that patients received treatment or did not

Group of patients evaluated in MW test	Variable			
	Gender	Marital status	Comorbidities	Addictions
(a) MW test including patients receiving any treatment	SF-36 (PF, RL, P, GH and Pcom) and CLDQ (AS, SS, AT and overall score)	-	SF-36 (RL, P, SF, EW, Mcom) and CLDQ (AS, AT and overall scores)	CLDQ (AS)
(b) MW test including patients without treatment	SF-36 (RL)	-	SF-36 (RL and Mcom)	SF-36 (P, EW, V, MH, Mcom) and CLDQ (SS)
(c) MW test for patients that were treated with duo therapy	SF-36 (RL, Pcom) and CLDQ (AS, SS, AC, overall scores)	CLDQ (FA)	CLDQ (AS, SS and overall scores)	CLDQ (AS and EF)
(d) MW test for patients that were treated with triple therapy	SF-36 (P)	SF-36 (GH)	SF-36 (RL, SF, EW, MH and Mcom)	-

Note: This table presents the statistical significant results from the sub analysis according to each variable using Mann-Whitney test (i.e. male vs female; Married/cohabiting vs. single/separated/widowed; comorbidities yes vs. no; and addictions yes vs. no). Each line indicate a different group of patients: (a) patient without treatment, (b) patients receiving treatment, (c) patient receiving duo therapy, (d) patients receiving triple therapy. For example the variable gender, the mean score from each domain was compared between male and female patients. The table present only the domains that were statistical significant (in parentheses) from the respective questionnaire, which in the specific case of the patients receiving triple therapy was observed only in the pain (P) domain of SF-36.

effects and have lower treatment duration<sup>33-38</sup>.

It is evident that most patients are asymptomatic during the natural course of the disease. However, the peak of viral prevalence occurs among individuals who are in the fifth decade of life; adult subjects who are in the

active phase of life. In this phase, it appears that hepatic cirrhosis is the most common symptom in 20 to 30% of patients with chronic infections. Subsequently, cirrhosis and hepatocellular carcinoma often develop in 1 to 4% of patients per year<sup>39-41</sup>.

Some authors point out that in addition to treatment, other factors can also influence the quality of life such as ethnicity, income, work, and educational level<sup>42</sup>. However, others declare that factors such as age, genotype, degree of fibrosis, do not seem to exert any effect on the quality of life<sup>24</sup>.

Despite the adaptation to the local reality where the study was conducted, the small sample size in some groups and the absence of additional control groups were considered limitations. To generalize the results, it is necessary to replicate this study in more States in Brazil. Additionally, other social economical aspects (such as monthly income and educational level), laboratory data (e.g., albumin, bilirubin, alanine and aspartate aminotransferase) and the time since the diagnosis (the stage of the disease) were not evaluated here. This last parameter could not be analyzed especially due to missing data. As the second generation DAA was not evaluated in this study, we suggest the evaluation of quality of life of hepatitis C patients receiving these drugs in Brazil.

## CONCLUSIONS

This study showed that, in some domains, there is a decrease in the quality of life in treated patients with CHC receiving interferon-based therapies, which is associated with a significant number of side effects and injections. Additionally, the quality of life was similar in patients receiving dual and triple therapies with first-generation DAAs. The data found in this study provided a better understanding of the quality of life of patients with hepatitis C and their needs, which will ensure better healthcare for those who are undergoing treatment.

## CONFLICT OF INTEREST

None declared.

## FINANCIAL SUPPORT

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## REFERENCES

- World Health Organization. Hepatitis C: fact sheet. Geneva: WHO; 2017. [cited 2017 Aug 08]. Available from: <http://www.who.int/mediacentre/factsheets/fs164/en/>
- Bianco T, Cillo U, Amodio P, Zanusi G, Salari A, Neri D, et al. Gender differences in the quality of life of patients with liver cirrhosis related to hepatitis C after liver transplantation. *Blood Purif*. 2013;36:231-6
- Fábregas BC, de Ávila RE, Faria MN, Moura AS, Carmo RA, Teixeira AL. Health related quality of life among patients with chronic hepatitis C: A cross-sectional study of sociodemographic, psychopathological and psychiatric determinants. *Braz J Infect Dis*. 2013;17:633-9.
- Orr JG, Homer T, Ternent L, Newton J, McNeil CJ, Hudson M, et al. Health related quality of life in people with advanced chronic liver disease. *J Hepatol*. 2014;61:1158-65.
- Sharif F, Mohebbi S, Tabatabaee H-R, Saberi-Firoozi M, Gholamzadeh S. Effects of psycho-educational intervention on health-related quality of life (QOL) of patients with chronic liver disease referring to Shiraz University of Medical Sciences. *Health Qual Life Outcomes*. 2005;3:81.
- Treloar C, Rance J, Backmund M. Understanding barriers to hepatitis C virus care and stigmatization from a social perspective. *Clin Infect Dis*. 2013;57 Suppl 2:S51-5.
- Bakas T, McLennon SM, Carpenter JS, Buelow JM, Otte JL, Hanna KM, et al. Systematic review of health-related quality of life models. *Health Qual Life Outcomes*. 2012;10:134.
- García HI, Vera CY, Lugo HL. Calidad de vida relacionada con la salud en Medellín y su área metropolitana, con aplicación del SF-36. *Rev Fac Nac Salud Publica*. 2013;32:26-39.
- Tudela LL. La calidad de vida relacionada con la salud. *Aten Primaria*. 2009;41:411-6.
- Whiteley D, Elliott L, Cunningham-Burley S, Whittaker A. Health-related quality of life for individuals with hepatitis C: a narrative review. *Int J Drug Policy*. 2015;26:936-49.
- Braga SF, Peixoto SV, Gomes IC, Acúrcio FA, Andrade EI, Cherchiglia ML. Factors associated with health-related quality of life in elderly patients on hemodialysis. *Rev Saude Publica*. 2011;45:1127-36.
- Campolina AG, Ciconelli RM. O SF-36 e o desenvolvimento de novas medidas de avaliação de qualidade de vida. *Acta Reumatol Port*. 2008;33:127-33.
- Bullinger M, Quitmann J. Quality of life as patient-reported outcomes: principles of assessment. *Dialogues Clin Neurosci*. 2014;16:137-45.
- Castro PC, Driusso P, Oishi J. Convergent validity between SF-36 and WHOQOL-BREF in older adults. *Rev Saude Publica*. 2014;48:63-7.
- Amodio P, Salari L, Montagnese S, Schiff S, Neri D, Bianco T, et al. Hepatitis C virus infection and health-related quality of life. *World J Gastroenterol*. 2012;18:2295-9.
- Gao R, Gao F, Li G, Hao JY. Health-related quality of life in Chinese patients with chronic liver disease. *Gastroenterol Res Pract*. 2012;2012:516140.
- Younossi ZM, Stepanova M, Zeuzem S, Dusheiko G, Esteban R, Hezode C, et al. Patient-reported outcomes assessment in chronic hepatitis C treated with sofosbuvir and ribavirin: the VALENCE study. *J Hepatol*. 2014;61:228-34.

18. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30:473-83.
19. Ciconelli RM, Ferraz MB, Santos W, Meinão I, Quaresma MR. Tradução para a língua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF-36 (Brasil SF-36). *Rev Bras Reumatol*. 1999;39:143-50.
20. Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut*. 1999;45:295-300.
21. Mucci S, Citero VA, Gonzalez AM, De Marco MA, Nogueira-Martins LA. Adaptação cultural do Chronic Liver Disease Questionnaire (CLDQ) para população brasileira. *Cad Saude Publica*. 2010;26:199-205.
22. Laucis NC, Hays RD, Bhattacharyya T. Scoring the SF-36 in orthopaedics: a brief guide. *J Bone Joint Surg Am*. 2015;97:1628-34.
23. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: scoping review. *SAGE Open Med*. 2016;4:2050312116671725.
24. Bezemer G, Van Gool AR, Verheij-Hart E, Hansen BE, Lurie Y, Esteban JI, et al. Long-term effects of treatment and response in patients with chronic hepatitis C on quality of life. An international, multicenter, randomized, controlled study. *BMC Gastroenterol*. 2012;12:11.
25. El Khoury AC, Vietri J, Prajapati G. Health-related quality of life in patients with hepatitis C virus infection in Brazil. *Rev Panam Salud Publica*. 2014;35:200-6.
26. Dan AA, Kallman JB, Srivastava R, Younoszai Z, Kim A, Younossi ZM. Impact of chronic liver disease and cirrhosis on health utilities using SF-6D and the health utility index. *Liver Transpl*. 2008;14:321-6.
27. Chang SC, Yang SS, Chang CC, Lin CC, Chung YC, Li TC. Assessment of health-related quality of life in antiviral-treated Taiwanese chronic hepatitis C patients using SF-36 and CLDQ. *Health Qual Life Outcomes*. 2014;12:97.
28. Schulz KH, Kroencke S, Ewers H, Schulz H, Younossi ZM. The factorial structure of the Chronic Liver Disease Questionnaire (CLDQ). *Qual Life Res*. 2008;17:575-84.
29. Cammà C, Petta S, Enea M, Bruno R, Bronte F, Capursi V, et al. Cost-effectiveness of boceprevir or telaprevir for untreated patients with genotype 1 chronic hepatitis C. *Hepatology*. 2012;56:850-60.
30. Shahid I, AlMalkiWH, Hafeez MH, Hassan S. Hepatitis C virus infection treatment: an era of game changer direct acting antivirals and novel treatment strategies. *Crit Rev Microbiol*. 2016;42:535-47.
31. Suzuki M, Ishikawa T, Sakuma A, Abe S, Abe H, Koyama F, et al. Evaluation of the health-related quality of life using the 36-item short form health survey in patients with chronic hepatitis C receiving pegylated interferon/ribavirin/telaprevir triple treatment. *Exp Ther Med*. 2016;12:3353-8.
32. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de DST, Aids e Hepatites Virais. Protocolo clínico e diretrizes terapêuticas para hepatite C e coinfeções. Brasília: Ministério da Saúde; 2015.
33. Ferreira VL, Assis Jarek NA, Tonin FS, Borba HH, Wiens A, Pontarolo R. Safety of interferon-free therapies for chronic hepatitis C: a network meta-analysis. *J Clin Pharm Ther*. 2016;41:478-85.
34. Ferreira VL, Tonin FS, Assis Jarek NA, Ramires Y, Pontarolo R. Efficacy of interferon-free therapies for chronic hepatitis C: a systematic review of all randomized clinical trials. *Clin Drug Investig*. 2017;37:635-46.
35. Younossi ZM, Stepanova M, Esteban R, Jacobson I, Zeuzem S, Sulkowski M, et al. Superiority of interferon-free regimens for chronic hepatitis C: the effect on health-related quality of life and work productivity. *Medicine (Baltimore)*. 2017;96:e5914.
36. Cho HJ, Park E. Quality of life of chronic hepatitis C patients and its associated factors. *Osong Public Health Res Perspect*. 2017;8:124-9.
37. Rei A, Rocha M, Pedroto I. Health-related quality of life in Portuguese patients with chronic hepatitis C. *GE Port J Gastroenterol*. 2017;24:68-78.
38. Armstrong AR, Herrmann SE, Chassany O, Lalanne C, Da Silva MH, Galano E, et al. The international development of PROQOL-HCV: an instrument to assess the health-related quality of life of patients treated for hepatitis C virus. *BMC Infect Dis*. 2016;16:443.
39. Kleinman L, Mannix S, Yuan Y, Kummer S, L'Italien G, Revicki D. Review of patient-reported outcome measures in chronic hepatitis C. *Health Qual Life Outcomes*. 2012;10:92.
40. Thompson JR. Emerging therapeutic options for the management of hepatitis C infection. *World J Gastroenterol*. 2014;20:7079-88.
41. Wiessing L, Ferri M, Grady B, Kantzanou M, Sperle I, Cullen KJ, et al. Hepatitis C virus infection epidemiology among people who inject drugs in Europe: a systematic review of data for scaling up treatment and prevention. *PloS one*. 2014;9:e103345.
42. Abdo AA. Health-related quality of life of Saudi hepatitis B and C patients. *Ann Saudi Med*. 2012;32:397-403.