Elbadry *et al. Egyptian Liver Journal* (2024) 14:14
https://doi.org/10.1186/s43066-024-00317-8

Egyptian Liver Journal

ORIGINAL RESEARCH ARTICLE

Open Access

Impact of treating chronic hepatitis C with direct acting antivirals on health-related quality of life: a real-life Egyptian experience

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Abstract

Background Chronic hepatitis C virus (HCV) infection negatively impacts health-related quality of life (HRQL). We aimed to assess patient-reported outcomes (PROs) to evaluate the impact of treating chronic HCV with directly acting antivirals (DAAs) on HRQL.

Methods PROs were assessed prospectively using the PROQOL-HCV questionnaire before (week 0), at the end (week 12), and after DAA treatment at week 24. HRQL was measured in six different dimensions: physical health, emotional health, future uncertainty, intimate relationships, social health, and cognitive functions.

Results A total of 500 HCV patients receiving DAAs were enrolled; of them, 399 were included in the analysis (median age 57 years, 59% females). HRQL increased significantly between baseline, end of treatment, and week 24 for all dimensions ($P < 0.001$), more often for physical health in females compared to males (OR = 1.69, 95% CI = 1.1–2.5), for future uncertainty among people with diabetes (1.75, 95% CI = 1.05–2.9), and for cognitive functions among obese patients (OR = 1.98; 95% CI = 1.1–3.3). Improvement in HRQL was less common for intimate relations among females (OR = 0.47; 95% CI = 0.3–0.7) and in patients with cirrhosis (OR = 0.35, 95% CI = 0.1–0.7). Improvement in HRQL was consistently higher in < 60 years compared to ≥ 60 years patients, with a significant difference in social health ($P < 0.001$) and future uncertainty ($P < 0.049$) HRQL domains.

Conclusion HRQL improved with DAA therapy, a relation consistent across all HRQL dimensions up to 12 weeks after the end of treatment.

Keywords Direct acting antivirals (DAAs), Health-related quality of life (HRQL), Patient-reported outcomes (PROs), Hepatitis C virus (HCV), Egypt

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Background

Hepatitis C virus (HCV) infection still acts as a major global health problem; it is estimated that more than 80 million are chronically infected with HCV worldwide [1]. In Egypt, more than 5 million individuals were positive for HCV antibodies (7% seroprevalence) in 2015 [2, 3]. As of 2023, Egypt has achieved remarkable progress, exceeding WHO targets for diagnosing and treating people living with HCV. The prevalence has been reduced to an estimated 0.38%, marking a significant victory in the fight against the virus [4] (WHO, 2024). Chronic HCV significantly affects the overall HCV burden as it progresses to advanced stages of liver disease, and consequently, it negatively impacts multiple aspects of health-related quality of life (HRQL) [5, 6]. HCV patients often report a broad range of physical and mental symptoms, including but not limited to fatigue, musculoskeletal pain, poor appetite, nausea, abdominal pain, cognitive impairment, depression, and anxiety [7].

Over the past few years, the treatment landscape for HCV has been changing rapidly, ending with the introduction of directly acting antiviral therapy (DAAs), in which a cure rate with more than 90% of chronically infected patients has been achieved [8]. DAAs allow less treatment duration, reduced toxicity, higher barriers to resistance, and better tolerance, especially in some groups like elder patients (adults ≥ 60) compared to previous treatments; however, some side effects such as fatigue, nausea, and headache are still reported [9, 10].

DAAs enhance HRQL due to treatment, symptom alleviation, and an increase in associated socioeconomic benefits. However, the associated toxicity negatively affects (HRQL). Our understanding of patients' experience with DAAs is limited to data derived from clinical trials. Although they provide information on DAA's effect on HRQOL, no enough evidence has been generated from the patient's perspective [11].

Several questionnaires have been developed and used to evaluate the HRQL of people with HCV, using patient-reported outcome (PRO) measures [12]. Among these questionnaires are the Hepatitis Quality of Life Questionnaire (HQLQ) [13], the Chronic Liver Disease Questionnaire (CLDQ) [14], the Liver Disease Quality of Life Instrument [15], Liver Disease Symptom Index-2.0 [16], and the Chronic Liver Disease Quality of Life (CLD-QOL) Questionnaire [17].

Egypt launched a comprehensive plan to eliminate HCV that was able to treat 4 million patients over the last few years with good results and acceptable safety profile in different groups of patients including elderly [18–20]. This huge campaign was conducted in correspondence to the elimination targets set by the WHO for the global elimination of viral hepatitis by 2030 [21]. While Shehata et al.'s study explored the impact of DAAs on HRQoL in Egyptian HCV patients, offering valuable insights into improvements in anxiety, depression, and cognitive function, further research is crucial to solidify these findings and elucidate broader generalizability [22]. This study aimed to assess the impact of DAA treatment on health-related quality of life (QOL) in adult Egyptian patients with chronic HCV, comparing both those aged 60 years and older and those younger than 60 years. This might involve using validated QOL questionnaires to measure changes in physical, mental, and social functioning before and after treatment, and to identify any potential age-related differences in the efficacy, tolerability, and QOL impact of DAA treatment between older and younger adult patients with chronic HCV as a primary aim, also to evaluate the real-life efficacy and tolerability of (DAA) treatment for chronic HCV infection in adults aged 60 years and older in Egypt. This includes assessing sustained virological response (SVR) rates, treatment completion rates, and adverse events associated with DAA therapy as a secondary aim.

Patients and methods

Study design and setting

This prospective, observational longitudinal cohort study included patients with chronic HCV being treated under the Egyptian National Guidelines. Patients were recruited from the outpatient clinic of the New Cairo Viral Hepatitis Treatment Center, affiliated to the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) between August 2016 and September 2019. Among the main advantages of this site is the accessibility to a diverse population through serving a large number of patients from different socioeconomic standards [23].

The cohort was furtherly divided into two groups, one with the exposure of interest (adults ≥ 60 years old patients) and another internal comparison group (adults aged 18–59 years). Inclusion/exclusion criteria for this study followed HCV treatment national guideline issued by NCCVH. Study inclusion criteria were as follows: (1) patients aged 18 years; (2) being treated with all-oral interferon-free, DAAs containing regimen; and (3) agreeing to participate in the study and signing the informed consent form. Exclusion criteria included any neurocognitive disorder/mental impairment, which could prevent patients from partaking in the QOL questionnaires, in addition to the presence of a chronic debilitating disease, malignancy (including HCC), or liver decompensation (as evidenced by the presence of ascites, encephalopathy, or bleeding esophageal varices).

Received treatment regimens and follow-up visits

Antiviral therapy was given according to the Egyptian NCCVH guidelines. The used treatment regimen was sofosbuvir (SOF)/daclatasvir (DCV) combination. This regimen is the mainstay of the large treatment project in Egypt, and the currently approved one until now. According to the applied guidelines, patients with more advanced forms of disease received, in addition, weight-based RBV (1000 [< 75 kg] to 1200 mg [> 75 kg]).

All patients in the cohort attended follow-up visits every 4 weeks as per national treatment guidelines, where they were interviewed for collecting data related to treatment efficacy and safety. Medications were to be dispensed during the scheduled monthly follow-up visits. All stated treatment and follow-up procedures were already taking place as per the national treatment program. No extra follow-up visits or treatments were added to the patient schedule during this study.

Measurements

Standard data collected (national treatment program)

For clinical information relating to the efficacy and safety of the treatments in the cohort participants, data collection was done using the standardized case report forms (CRF), routinely used by the national treatment program. There are existing CRF for both baseline and follow-up visits which include the following variables.

Baseline visit Sex, age, treatment status (with details of previous treatment if any), weight, height, BMI, alcohol and tobacco intake, IV drug use, hypertension, diabetes (and treatment of), hepatic encephalopathy, hepatocellular carcinoma, special situations (ex., dialysis, post-transplant), HCV RNA (with quantification), liver function tests (i.e., ALT, AST, AFP, albumin, total bilirubin, indirect bilirubin, TSH, creatinine), blood tests (i.e., WBC, ANC, Hb, platelets, PC/INR), ANA, glucose, HbA1c, triglycerides, HDL, LDL, HB antigen, ECG, HIV, abdominal ultrasound details (including date, the status of liver and PV, presence of ascites or focal lesions), fib-4 calculation, child–pugh score calculation, contract type for treatment payment, and treatment decisions.

Follow-up visits HCV RNA (with quantification), to evaluate virological response, liver function tests (i.e., ALT, AST, albumin, total bilirubin), blood tests (i.e., WBC, ANC, Hb, platelets, PC or INR), whether or not there has been blood sample storage, side effects experienced, treatment decision (continue, stop, dose changes, etc.).

Additional data that was collected in the course of the study

During the baseline visit, some extra data was collected regarding the medical history of all patients involved in this cohort study using a short questionnaire. Furthermore, during scheduled follow-up visits, an extra emphasis was placed on collecting data regarding side effects being experienced and concomitant treatments using a short questionnaire.

The patient-reported outcome quality of life survey for HCV (PROQOL-HCV) was developed and psychometrically tested through a condensate review of literature and interview with treatment specialists and patients [24]. PROQOL-HCV has six dimensions: physical health, emotional health, future uncertainty, intimate relationships, social health, and cognitive functions. For each dimension, a set of questions was asked to participants who provided answers in five categories from "never" to "always." The answers were translated into scores ranging from 0 to 100, with higher scores reflecting higher HRQL. PROQOL-HCV has been validated among patients with HCV in France, Brazil, and Australia [25, 26]. The questionnaire was translated into Arabic and its convergent validity and internal reliability were tested. The Arabic version of the PROQOL-HCV has satisfactory validity and reliability among Egyptian HCV patients. Cronbach's alpha coefficient for the Arabic PROQOL-HCV's multi-item scales ranged from 0.85 to 0.96. A confirmatory analysis gives an RMSEA of 0.105 and a CFI of 0.825, which is acceptable [27].

Specific study procedures

Patients were then interviewed face-to-face to complete the questionnaire in the outpatient clinic during the visit. Three trained interviewers were responsible for conducting the face-to-face patient interviews in order to complete the PROQOL questionnaire at each visit. The questionnaires were paper-based.

Data were collected at three-time points: (1) baseline (week 0 prior to initiating therapy); (2) end of treatment (EoT) (week 12 after initiating therapy); (3) at time of assessing SVR12 (week 12 after EoT). At pretreatment visits, patients were assessed to confirm their eligibility to start the HCV therapy.

Study activities and procedures are detailed in Table 1.

Statistical methods

Descriptive statistics were provided for outcomes (HRQL) and explanatory factors (demographic and biomedical data), including age, sex, comorbidities, HCV disease-related factors and test results, and patient's status regarding HCV treatment and concomitant medications. Descriptive statistics were computed to

Table 1 Study schedule: treatment and data collection

	Treatments Given		Data Collection							Quality of Life Questionnaire
	12 Wk Dual Therapy	24 Wk Dual Therapy	PCR	Baseline form	Medical History	Standard follow-ups visit form		Detailed side effects, concomitant medications		
						12 Wk Dual	24 Wk Dual	12 Wk Dual Therapy	24 Wk Dual Therapy	
Enrolment			X	X	X					X
W0	X	X				X	X	X	X	
W4	X	X	X			X	X	X	X	
W8	X	X				X	X	X	X	
W12[a]	X	X	X			X	X	X	X	X (12 Wk only)
W16		X					X		X	
W20		X					X		X	
W24[b]		X	X			X (SVR)	X	X	X	X (12 &24 Wk)
W36[c]			X (24 Wk only)				X (SVR)		X	X (24 Wk only)
Unscheduled						X	X	X	X	

BLUE highlighted sections are new as per this study; in GREY follows NTP standard procedure

[a] Week 12 corresponding EOT

[b] Week 24 corresponding to SVR12

[c] Week 36 corresponding to SVR12 after the end of treatment for those patients whose treatment course was 24 wks

summarize data and represent participants' baseline demographic and clinical characteristics. Continuous variables were summarized using the median and interquartile range, while categorical variables were summarized as counts and proportions. Pearson Chi-squared and Student *t*-test were used for two-group comparisons. Paired *t*-test was used to analyze the association between HRQL at baseline, EOT, and SVR12. The score for each dimension at baseline was compared between categories of patient's characteristics (e.g., age, sex, comorbidities) using a *t*-test. Then, the score for each dimension was compared between baseline, EOT, and SVR12 using a paired *t*-test. Since the difference between HRQL at baseline, EOT, and SVR12 did not follow a normal distribution, we chose a binary outcome (improvement/no improvement) and a logistic regression model to study the characteristics (age, sex, comorbidities) associated with HRQL improvement (difference in SVR12, EOT, and baseline scores > 0). Variables associated with improvement in univariable analysis with *P* values > 0.2 were introduced in multivariable models. *P* values < 0.05 were considered statistically significant.

Radar plots incorporating the six dimensions were computed in order to assess overall HRQL. The surface area delimited by the radar plots was compared across baseline characteristics, and between baseline, EOT, and SVR12, by Student *t*-test and paired *t*-test, respectively. Finally, the mean change in surface area between baseline, EOT, and SVR 12 was compared across the characteristics of patients by Student *t*-test. Data Analysis and Statistical Software for Professionals (STATA-14) were used to generate the results.

Results

A total of 500 subjects were enrolled over the study period, and 101 subjects were excluded from the final analysis due to missing follow-up at one or more visits (45 patients), missing data at one or more visits (53 patients), while more three patients were excluded because of the missed SVR 12 data. The majority of the study patients (98.99%) achieved SVR 12. Figure 1 shows the patients' recruitment flowchart.

Participants' demographic and medical characteristics

The median age of the study participants was 57 years, and 59% were females. Nineteen percent, 23%, and 71% of the participants suffered from hypertension, diabetes, and obesity (BMI ≥ 30 kg/m^2) as comorbidities, respectively, while 17% were smokers. Cirrhosis was detected in 15% of the participants, 58% had abnormal liver functions, and thrombocytopenia (platelet count × 1000/L < 150) was found in 21% of the cases. FIB-4 score was more than 3.25 (indicating advanced fibrosis or cirrhosis) in 21% of the participants. Alpha-fetoprotein value (< 10 ng/mL), AST (≥ 40 IU/L), and ALT (≥ 56 IU/L) were found in 79%, 49%, and 29% of the cases, respectively. RBV was added to treatment regimens in 19% of the participants. Regarding previous exposure to antiviral therapy, 94% of the participants were HCV treatment-naïve, while the remaining 6% were interferon experienced. Table 2 summarizes the demographic and clinical characteristics of the study participants.

Characteristics of adults ≥ 60 years and adults < 60 years old patients

Regarding the age of participants, 54% of patients were < 60 years old. Comparison between the characteristics of adults < 60 years and adults ≥ 60 years old patients at baseline shows a significant difference in several characteristics, including sex ($P < 0.001$, OR = 2.5, 95% CI = 1.6–3.7), hypertension ($P < 0.001$, OR = 7.1, 95% CI = 3.8–13.3), liver condition (normal, abnormal, or cirrhotic, $P < 0.001$, OR = 3.3, 95% CI = 1.8–6.0), liver enzymes including normal or abnormal AST levels ($P < 0.01$, OR = 1.6, 95% CI = 1.1–2.4), presence of thrombocytopenia ($P < 0.001$, OR = 2.9, 95% CI = 1.7–4.8), and AFP level ($P < 0.01$, OR = 1.9, 95% CI = 1.1–3.1). Table 3 shows the comparison of the demographic and clinical characteristics between the adults ≥ 60 years and adults < 60 years old patients.

Comparison of QOL between adults ≥ 60 and adults < 60 years patients

Change in QOL among the adults ≥ 60 years and adults < 60 years old patients were assessed at the three time points of data collection (baseline, EOT, and SVR 12 weeks) and presented in Table 4. HRQL increased significantly between baseline and week 24 for all dimensions ($P < 0.001$), more often for physical health in females compared to males (OR = 1.69, 95% CI = 1.1–2.5), for future uncertainty among people with diabetes (1.75, 95% CI = 1.05–2.9), and for cognitive functions among obese patients (OR = 1.98; 95% CI = 1.1–3.3). Improvement in HRQL was consistently higher in adults < 60 years compared to adults ≥ 60 years patients, with a significant difference in social health ($P < 0.001$) and future uncertainty ($P < 0.049$) HRQL domains (Table 5).

Overall, HRQL incorporating the six dimensions

All six HQRL dimensions are incorporated in one measure using radar plots. The surface area of each radar plot corresponds to the HRQL score. The radar plots in Fig. 2 show the difference in QoL scores at baseline and their association with the characteristics of the study patients. Additionally, Table 1 of the annex shows the results of a

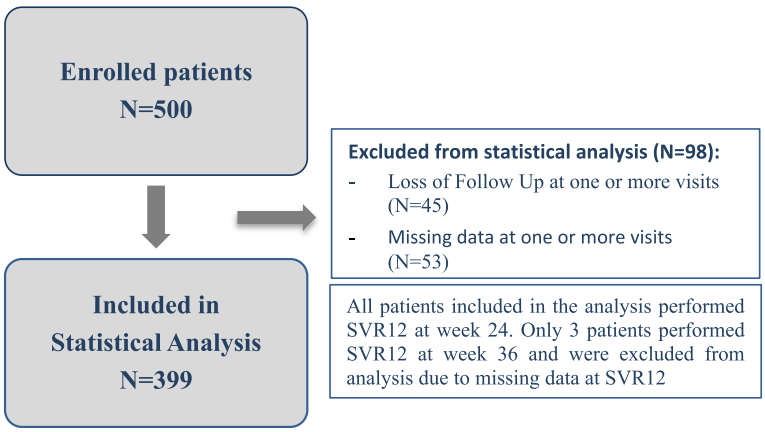

Fig. 1 Patient recruitment flowchart

Table 2 Baseline demographic, clinical characteristics, and laboratory data of the enrolled patients

Baseline characteristics *n* = 399	***n*, % for categorical values**	**Mean, SD for continuous variables**
Age (years)		52 (14.5)
Adults < 60	214 (54)	
Adults ≥ 60	185 (46)	
Gender		
Male	163 (41)	
Female	236 (59)	
Comorbidity: **hypertension**		
No	223 (82)	
Yes	73 (18)	
Missing	1	
Comorbidity: **diabetes**		
No	307 (77)	
Yes	91 (23)	
Missing	1	
BMI (kg/m^2)		29.8 (6.1)
Missing		204
Comorbidity: **obesity** (BMI ≥ 30)		
No	115 (29)	
Yes	287 (71)	
Smoking status		
Smokers	50 (17)	
Non-smokers	242 (83)	
Missing	105	
Hepatic condition (based on clinician's decision)		
Normal	107 (27)	
Abnormal	230 (598)	
Cirrhotic	61 (15)	
Missing	1	
FIB-4 (indicator of cirrhosis)		2.3 (1.9)
< 3.25 (IU)	316 (79)	
≥ 3.25 (IU)	85 (21)	
Missing	1	
Thrombocytopenia		
No (platelet count × 1000/L ≥ 150)	317 (79)	
Yes (platelet count × 1000/L < 150)	85 (21)	
HCV serum concentration (IU/mL × 10e + 06)		6.3 [1.6, 20]
Platelet count ($\times 10^9$/L)		
Missing		200.8 (69.3) 5
Alfa Feto-protein		
< 10 ng/mL	311 (79)	
≥ 10 ng/mL	87 (21)	7.9 (12.6)
Missing	2	
Liver enzymes: AST		
Normal level (< 40 IU/L)	204 (51)	
Abnormal level (≥ 40 IU/L)	195 (49)	48.4 (31.7)
Liver enzymes: ALT		
Normal level (< 56 IU/L)	281 (71)	

Table 2 (continued)

Baseline characteristics $n=399$	*n*, % for categorical values	Mean, SD for continuous variables
Abnormal level (≥ 56 IU/L)	116 (29)	49.7 (35.5)
Treatment status		
Naïve	374 (94)	
Experienced	23 (6)	
Missing	2	
Ribavirin in treatment combination		
No	322 (81)	
Yes	75 (19)	

multivariable analysis of the association between QOL improvement across the visits and patient characteristics. In the physical health dimension, the difference was significant in gender, where the OR among females was 1.8 compared to males, 95% CI (1.1–2.8), *P* 0.009. Tables 2 and 3 of the annex show the changes in QOL score in each domain at the three times of data collection (baseline, EOT, SVR12) between adults < 60 years and adults ≥ 60 years patients. The change was found to be significant in the social health domain, where the OR among adults ≥ 60 years was 0.3 compared to adults < 60 years, 95% CI (0.1–0.4), $P < 0.001$.

Discussion

This cohort evaluates HRQL among HCV patients undertaking DAA treatment in real-life settings in Egypt. PROQOL-HCV was used as an HCV-specific and HRQL-validated tool to evaluate comprehensive PROs incorporating multiple dimensions while considering the shift in the standard of care treatment to include DAAs, disease stage, and population-specific characteristics.

QOL at baseline varied according to specific characteristics: Based on the analysis of the PROs provided by the 399 subjects included in the analysis, the results of the evaluation of HRQL show that baseline values of certain patient characteristics varied, including the following demographic and clinical characteristics: age, gender, comorbidities; hypertension, diabetes, obesity, thrombocytopenia, cirrhosis, smoking status, tumor markers including AFP, liver enzymes; AST and ALT, and variables related to treatment such as treatment status (DAAs naïve or not), and if RBV is included in treatment combination. Differences regarding overall HRQL at baseline were significant in the following characteristics: gender, hypertension, obesity, and RBV treatment. Individual assessment of each HRQL dimension showed that the differences varied across the six dimensions; however, they remained relatively consistent. Also, these differences were significant for liver enzymes.

QOL at baseline varied between the population of adult patients aged 60 years or older and that aged less than 60 years. Recognizing the significant heterogeneity within the older adult population is essential. Chronological age alone does not capture individual differences in functional status, cognitive abilities, and personal preferences. A comprehensive geriatric assessment that evaluates physical, cognitive, functional, psychological, and social domains is crucial for understanding individual needs and tailoring interventions to optimize QOL [28]. Finally, understanding the multifaceted impact of age on QOL is vital for making informed clinical decisions that prioritize not only clinical outcomes but also the well-being and satisfaction of older adults. By incorporating age-specific considerations, employing appropriate QOL measures, and engaging in shared decision-making, clinicians can ensure treatment plans effectively address the unique needs and priorities of each individual [29]. Evaluation of HRQL showed that certain characteristics varied between both populations at baseline, including the following demographic and clinical characteristics: gender, hypertension, liver condition, thrombocytopenia, AFP, and AST levels.

Improvement in QOL with DAA therapy

Recording of PROs during treatment with DAAs demonstrates their effect on HRQL by comparing the improvement in HRQL between baseline, EOT, and SVR12. Results of this study show evidence of an association between undertaking DAA therapy and improvement in HRQL. Upon evaluation of the association between DAA therapy and HRQL, significant improvement in HRQL was found. Improvement in HRQL varied in each HRQL dimension; however, the correlation remained consistent with the overall HRQL improvement, which was highly significant across the six dimensions. Improvement in

Table 3 Comparison between demographic, clinical characteristics, and laboratory data of adults ≥ 60 years and adults < 60 years old patients

Baseline characteristics *n* = 399	*n* (%) for categorical values		OR for categorical values (95% CI)	*P* value	Mean (SD) for continuous variables		RR for continuous values (95% CI)	*P* value
	Adults < 60 years (*n* = 211)	Adults ≥ 60 years (*n* = 188)			Adults < 60 years (*n* = 211)	Adults ≥ 60 years (*n* = 188)		
Age (years)					41 (10.8)	65 (3.6)		
Age (years) *n* = 399								
Adults < 60	211 (53)	188 (47)						
Adults ≥ 60								
Gender								
Male	107 (51)	55 (29)	2.5 (1.6–3.7)	< 0.001				
Female	104 (49)	133 (71)						
Comorbidity: **hypertension**			7.1 (3.8–13.3)	< 0.001				
No	197 (93)	124 (66)						
Yes	14 (7)	63 (34)						
Comorbidity: **diabetes**			1.1 (0.7–1.7)	0.76				
No	163 (77)	142 (76)						
Yes	48 (23)	45 (24)						
Missing	0	1						
BMI (kg/m^2)								
Missing					29.8 (6.1) 109	31.4 (6.5) 95	1.4 (1.1–1.9)	< 0.01
Comorbidity: **obesity** (BMI ≥ 30)								
No	76 (75)	46 (50)	2.3 (1.6–5.5)	< 0.001				
Yes	26 (25)	47 (51)						
Missing	109	95						
Smoking status								
Smokers	176 (83)	63 (81)	1.1 (0.6–2.2)	0.75				
Non-smokers	35 (17)	15 (19)						
Missing	0	110						
Hepatic condition *(based on clinician's decision)*								
Normal	80 (38)	27 (26)	3.3 (1.8–6.0)	< 0.001				
Abnormal	114 (54)	119 (59)						
Cirrhotic	17 (8)	42 (15)						
FIB-4								
Missing					2.31 (1.9) 1		2.1 (1.7, 2.5)	< 0.001
FIB-4 *(Indicator of cirrhosis)*								
< 3.25 (IU)	193 (92)	121 (64)	6.2 (3.5–11.2)	< 0.001				
≥ 3.25 (IU)	17 (8)	67 (36)						
Missing	1	0						
Platelet count (× 10^9/L)					216.4 (68.6)	182.9 (65.9)	1.6 (1.4, 2.0)	< 0.001
Thrombocytopenia								
No (platelet count × 1000/L ≥ 150)	184 (87)	132 (70)	2.9 (1.7–4.8)	< 0.001				
Yes (platelet count × 1000/L < 150)	27 (13)	56 (30)						
HCV serum concentration								
(IU/mL × 10e + 06)					2.1 (5.4)	2.0 (6.1))		
Alfa Feto-protein (10 ng/mL)								
Missing					10.2 (15.7) 3	5.9 (8.4) 2	1.4 (1.1, 1.7)	0.005

Table 3 (continued)

Baseline characteristics *n* = 399	*n* (%) for categorical values		OR for categorical values (95% CI)	*P* value	Mean (SD) for continuous variables		RR for continuous values (95% CI)	*P* value
	Adults < 60 years (*n* = 211)	Adults ≥ 60 years (*n* = 188)			Adults < 60 years (*n* = 211)	Adults ≥ 60 years (*n* = 188)		
Alfa Feto-protein								
< 10 ng/mL	176 (85)	138 (74)	1.9 (1.2–3.2)	< 0.01				
≥ 10 ng/mL	32 (15)	48 (26)						
Missing	3	2						
Liver enzymes: AST								
(IU/L)					44.2 (27.3)	53.2 (35.5)	1.3 (1.0, 1.6)	0.01
Liver enzymes: AST								
Normal level (< 40 IU/L)	121 (57)	85 (45)	1.6 (1.1–2.4)	< 0.01				
Abnormal level (≥ 40 IU/L)	90 (43)	103 (55)						
Liver enzymes: ALT								
(IU/L)					49.5 (35.4)	49.8 (35.7)	0.9 (0.8, 1.2)	0.66
Liver enzymes: ALT								
Normal level (< 56 IU/L)	148 (70)	135 (72)	0.9 (0.6–1.4)	0.71				
Abnormal level (≥ 56 IU/L)	63 (30)	53 (28)						
Treatment status								
Naïve	194 (92)	182 (97)	3.3 (1.9–5.9)	< 0.001				
Experienced	17 (8)	6 (3)						
Ribavirin in treatment combination								
No	**151 (72)**	**175 (93)**	**0.2 (0.1–0.4)**	**< 0.001**				
Yes	60 (28)	13 (7)						

To evaluate the effect of the various demographic and clinical characteristics among adults ≥ 60 years and adults < 60 years, *Z*-test for odds ratio (OR, 95% CI) was used for the categorical variables to compare demographic and clinical characteristics among adults ≥ 60 years and adults < 60 years old patients, while *Z*-test for risk ratio (RR, 95% CI) was used for the categorical variables. A value of $P < 0.05$ was considered to be significant

physical health may be partially related to viral suppression and/or HCV eradication after treatment with DAAs, which was achieved in all subjects. However, it was also attributed to improvement in liver function, which would primarily manifest in patients with cirrhosis and other extra-hepatic manifestations of HCV infection. Improvement was also significantly better among subjects with no comorbidities such as hypertension, diabetes, and obesity (given that 71% were obese, which is significant compared to the adult prevalence rate in Egypt of < 33% [30].

Comparison of the same association between DAA therapy and HRQL among adults aged 60 years and older and adults less than 60 years showed significant improvement in HRQL. This improvement varied according to the clinical and demographic and clinical characteristics throughout baseline, EOT, and SVR12 visits between the population of adults aged 60 years or older and that aged less than 60 years. This comparison showed that the improvement in HRQL was higher in patients less than 60 years compared to those aged 60 years or older in the following characteristics: gender, where females showed better improvement compared to males aged 60 years or older, and in hypertensive patients less than 60 years compared to non-hypertensive patients aged 60 years or older, and in obese patients.

Overall improvement in HRQL varied between both populations of adults less than 60 years and that aged 60 years or older, where better improvement in 4 HRQL dimensions was found among patients less than 60 years compared to those aged 60 years or older. This variation in the improvement of HRQL between adults aged 60 years and older and adults less than 60 years was found to be most significant in the intimate relation dimension, as improvement in intimate relation among the population aged less than 60 years was found to be significant compared to that among adults aged 60 years or older. Such association may be attributed to a negative effect of aging on the perception of patients of certain relevant HRQL aspects; an influence by cultural and religious beliefs was inferred from responses to future uncertainty-related items, and the relation with social health may be attributed to a higher level of professional engagement associated with fear of discrimination, and

Table 4 QOL (overall and each domain); comparison between adults ≥ 60 years and adults < 60 years old participants

Each domain of QOL; comparison between adults ≥ 60 years and adults < 60 years				
QOL (adults < 60 years and adults ≥ 60)	*N* (%)	Mean QoL score (0–100), SD	Mean difference	*P* value
Physical health (*N* = 399)				
Adults < 60 years	211 (53)	76.9, 22.1	3.4	0.13
Adults ≥ 60 years	188 (47)	73.4, 24.5		
Emotional health (*N* = 399)				
Adults < 60 years	211 (53)	85.5, 18.9	2.2	0.2
Adults ≥ 60 years	188 (47)	83.3, 21.3		
Future uncertainty (*N* = 399)				
Adults < 60 years	211 (53)	76.4, 21.4	− 2.1	0.3
Adults ≥ 60 years	188 (47)	78.5, 22.3		
Intimate relation (*N* = 395)				
Adults < 60 years	211 (53)	85.4, 24.5	− 6.5	**0.003**
Adults ≥ 60 years	184 (47)	92, 18.02		
Social health (*N* = 390)				
Adults < 60 years	204 (52)	68.1, 13.6	0.03	0.9
Adults ≥ 60 years	186 (48)	68.1, 18.3		
Cognitive function (*N* = 394)				
Adults < 60 years	209 (52)	86.8, 17.6	− 2.2	0.2
Adults ≥ 60 years	185 (48)	89, 22.4		
Overall QOL; comparison between adults ≥ 60 years and adults < 60 years				
Patient characteristics (*N* = 381)	*N* (%)	Mean QoL score (mean = 80.6)	Mean difference	*P* value
Age				
Adults < 60 years	201 (52)	80.4	− 0.5	0.7
Adults ≥ 60 years	180 (48)	80.9		
Gender				
Male	156 (41)	82.7	3.5	**0.01**
Female	225 (59)	79.2, 16.1		
***Comorbidity*: hypertension**				
No	306 (80)	81.3	3.7	**0.04**
Yes	74 (20)	77.6		
Missing	1			
***Comorbidity:* diabetes**				
No	292 (76)	80.6	0.1	0.9
Yes	88 (24)	80.5		
Missing	1			
***Comorbidity:* obesity**				
No (BMI > 30)	110 (29)	83.1	3.6	**0.02**
Yes (BMI < 30)	271 (71)	79.5		
Cirrhosis				
No (normal + abnormal)	328 (86)	80.4	− 1	0.6
Yes	53 (14)	81.4		
Thrombocytopenia				
No (platelet count > 150)	302 (79)	80.7	0.7	0.6
Yes (platelet count > 150)	79 (21)	80		
Alfa Feto-protein				
< 10 ng/mL	302 (80)	80.6	0.6	0.7
≥ 10 ng/mL	74 (20)	80.1		
Missing	5			

Table 4 (continued)

Liver enzymes: AST				
Normal level (< 40 IU/L)	193 (51)	80.1	− 1	0.5
Abnormal level (≥ 40 IU/L)	188 (49)	81.1		
Liver enzymes: ALT				
Normal level (< 56 IU/L)	272 (71)	79.8	− 2.8	0.08
Abnormal level (≥ 56 IU/L)	109 (29)	82.5		
RBV treatment included				
No	315 (82)	81.3	4	**0.03**
Yes	66 (18)	77.3		

Table 5 Improvement in QOL scores between baseline, EOT, and SVR12

QoL dimension (*n* = 399)	% with better QoL at EoT, at SVR12 (*n*)	Mean QoL score (0–100)	Mean difference	95% CI	*P* value
Physical health					
Baseline		75.2			
EoT	45 (179)	79.5	9.5	7.2, 11.7	< 0.0001
SVR-12	62 (248)	89	13.8	11.3, 16.2	< 0.0001
Emotional health					
Baseline		84.3			
EoT	48 (190)	90.4	6.1	3.8, 8.4	< 0.0001
SVR-12	54 (218)	96.2	11.8	9.7, 13.9	< 0.0001
Missing	1				
Future uncertainty					
Baseline		77.5			
EoT	54 (216)	85.3	7.8	5.4, 10.2	< 0.0001
SVR-12	64 (255)	91.4	13.9	11.6, 16.2	< 0.0001
Missing	1				
Intimate relation					
Baseline		88.5			
EoT	25 (97)	93.5	5.1	2.8, 7.3	< 0.0001
SVR-12	28 (112)	97.1	8.6	6.4, 10.9	< 0.0001
Missing	12				
Social health					
Baseline		68.2			
EoT	31 (117)	70.1	2.6	0.7, 4.5	< 0.01
SVR-12	32 (126)	71.7	3.6	1.6, 5.5	< 0.001
Missing	12				
Cognitive function					
Baseline		87.9			
EoT	26 (98)	90.4	2.4	0.2, 4.7	< 0.05
SVR-12	29 (114)	92.6	4.7	2.5, 6.9	< 0.0001
Missing	19				

negative perception of self-image in society across the younger population. In the social health dimension, the responses of the study patients to the questionnaire during the study showed that the improvement in HRQL was associated with certain cultural traits such as strong family bonding and support during treatment. Although the improvement in HRQL after DAA therapy varied among study participants, no difference was found in overall HRQL improvement with regard to patient characteristics. Moreover, in some dimensions, HRQL

Fig. 2 QOL scores at baseline based on patient characteristics

improvement was significantly better for some characteristics; however, such relation was inconsistent among the six dimensions between adults aged 60 and older and adults less than 60. Results of previous studies similarly show that HRQL improvement is associated with age and that patients aged ≥ 65 should be carefully monitored compared to younger patients [31].

The fluctuation in overall HRQL improvement across the 6 HRQL dimensions and between adults aged 60 years and older and adults less than 60 years across baseline, EOT, and SVR12 may be associated with healthcare provision-related factors; these mainly involve follow-up during and after treatment. The study results and findings suggest that improving the patient follow-up process is needed as it impacts the patient's well-being. Comparison with the results from previous studies showed a consistent positive association between fibrosis stage and HRQL impairment in the physical domain at baseline, while significant improvements in most HRQL domains were observed at EOT and SVR12, regardless of fibrosis stage [32]. The impact of DAAs-based HCV treatment on PROs and liver-related outcomes in real-world settings was described in some reports. In a real-life prospective cohort from the USA, the investigators used the Short Form (SF)-36 as well as 3 other approved instruments. The authors found a 30% increase in SF-36 vitality score from baseline to SVR12: 63 versus 82 ($P=0.001$, $N=111$). At SVR12, scores improved in 24 of the 25 PRO domains ($P=0.05$). Almost all of the increases were greater than 5%, indicating clinical significance. Patients with no or early fibrosis before therapy improved in 22 domains compared to those with advanced fibrosis [33].

Additionally, a real-life prospective cohort from Italy that used the HQLQv2 questionnaire, which also assessed hepatitis-specific functional limitations and distress, showed that DAAs improves HCV patients' general quality and psychological state [34]. Comparison of the results of this study to those of studies that aimed to evaluate the impact of DAAs on HRQL and in HIV/HCV co-infected patients showed that HCV treatment led to substantial improvements in physical health in 45% and cognitive function [35, 36]. Furthermore, HRQL improvements were similar to those of patients with HCV mono-infection despite having lower HRQL at baseline [37]. Improvement in HRQL is not conclusive in studies measuring its change following DAAs. A large German study that included 1180 HCV patients measured HRQL using Short-Form 36 (SF-36) questionnaires. Researchers investigated potential predictors of HRQL changes. Only half of the patients in the study saw a clinically significant improvement in their mental and physical component summary ratings. They discovered that fatigue ($P=0.023$, OR = 1.518), elevated GPT levels ($P=0.005$, OR = 0.626), and RBV-containing therapy regimens ($P=0.001$, OR = 1.692) were all linked to clinically significant deterioration in HRQL following DAA therapy [38]. The research on the relationship between post DAA treatment of HCV (SVR) and HRQOL has yielded valuable insights, but there are still areas that need further exploration. These are some potential directions for future research: (1) long-term effects: most studies have followed patients for a limited period after achieving SVR. More research is needed to understand the long-term impact of SVR on HRQOL, particularly beyond 5 years. Also, investigate the potential delayed benefits or detriments to HRQOL as patients age and other health conditions emerge. (2) Subgroup analysis: current research often combines diverse patient populations. Future studies could delve deeper into specific subgroups, such as patients with co-morbidities, specific HCV genotypes, or different treatment regimens, to identify nuanced relationships between SVR and HRQOL. Also, explore the impact of socio-economic factors, cultural aspects, and access to healthcare on HRQOL outcomes for different patient groups. (3) Specific HRQOL domains: while most studies use general HRQOL measures, future research could explore the impact of SVR on specific domains like fatigue, sleep quality, cognitive function, or mental health using targeted assessments. Also, investigate the potential mechanisms underlying these specific HRQOL improvements or lingering issues post-SVR.

While some research has explored the link between HCV treatment and HRQOL, further investigation is needed to understand the nuanced impact of different treatment regimens on patients' quality of life. These are some potential directions for future research: (1) direct comparisons of regimens: conduct head-to-head studies comparing HRQOL outcomes in patients receiving different treatment regimens, considering factors like duration, side effects, and patient preferences. Also, include newer, interferon-free regimens alongside traditional options to provide a comprehensive picture of current treatment landscape. (2) Subgroup analysis based on patient characteristics: analyze HRQOL data within subgroups defined by relevant factors like treatment history, comorbidities, age, or genotype. This can reveal how specific patient profiles respond differently to different regimens. Also, investigate potential interactions between treatment type and individual characteristics that influence HRQOL outcomes.

Limitations

Need for a standardized methodology for analysis

Following the literature review and the implementation of the analysis plan adapted in this study, it is evident that the development of a standardized methodology

and tools for the evaluation and analysis of HRQL in HCV patients is required in order to improve the evaluation process, provide a standardized tool that maximizes research outcomes, establish generalizability, ensure validity, and reduce risk of bias that may arise due to various factors related to the population, treatment, and/or study context.

Potential limitations

Limitations and potential risks of bias regarding the assessment of the variables related to treatment include lack of comparable intervention, reported side effects, and the amount of missing data and loss of follow-up that might have increased the risk of information bias. Also, the large number of comparisons may increase the risk of error in estimate evaluation due to variations in the data and the generated results.

Conclusion

This study results provide evidence that HRQL varied according to the characteristics of HCV patients as shown at baseline, and this variation was also found between patients aged 60 years and older and patients less than 60 years. The study results show that PROs significantly improved with DAA therapy, a relation that was consistent across the 6 HRQL dimensions. Accordingly, DAAs result in short and long-term improvement of HRQL. Clinical outcomes at EOT and SVR12 were considered the primary endpoints of clinical trials; however, PROs have demonstrated their importance as endpoints that must be considered with clinical outcomes. The study findings provide an insight into the significance of HRQL assessment as an essential aspect of the treatment process due to its critical role in affecting well-being and clinical outcomes during and after HCV treatment. Moreover, PROs reflect the perspective of the patient in terms of HRQL, which should be accounted for by healthcare providers in order to optimize HCV treatment outcomes.

Abbreviations

AFP	Alpha-fetoprotein
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
CLDQ	Chronic Liver Disease Questionnaire
CLD-QOL	Chronic liver disease quality of life
DAAs	Direct acting antiviral therapy
EOT	End of treatment
HCV	Hepatitis C virus
HRQL	Health-related quality of life
ICH-GCP	The International Council for Harmonization of Technical Requirements for; Pharmaceuticals for Human Use—Good Clinical Practice
IRB	Institutional Review Board
NTP	National treatment program
PROQOL-HCV	Patient-reported outcome quality of life survey for HCV
PROs	Patient-reported outcomes
RBV	Ribavirin
SVR	Sustained virological response
TCP	Thrombocytopenia

Acknowledgements

None.

Authors' contributions

MEK, ME, and AF designed the study. MD created the original tool. NY translated and validated the tool. SAS, HE, and KS collected the data. MB, AF, ER, AV, and YM analyzed the data. ME, MB, NY, and MEK wrote the first draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

Funding

This is a non-funded work.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki after approval from the Institutional Review Board (IRB) for human subject research at the National Hepatology and Tropical Medicine Research Institute (Serial: 28-2015) and Egyptian Ministry of Health. Written informed consent was obtained from the subjects after explaining the study's aim and completing the consenting process.

Consent for publication

All authors agree to the journal rules for publications

Competing interests

The authors declare no competing interests.

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Received: 29 November 2023 Accepted: 14 February 2024
Published online: 27 February 2024

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