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Concise review

The impact of direct-acting antivirals on quality of life in patients with hepatitis C virus infection: a meta-analysis

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ABSTRACT

Introduction and Objectives: It is well known that the quality of life (QoL) of patients with chronic hepatitis C (HCV) is lower than that of the general population and that therapy with direct-acting antivirals (DAA) for HCV is safe and effective. However, data on the QoL of patients are scanty. The purpose of this study was to assess the effect of DAA drugs on patients' QoL.

Methods: The literature included in this meta-analysis was due in March 2021. The random effect model of heterogeneous data and the fixed effect model of homogeneous data were used to analyze the data. QoL had to be evaluated using the Short Form Health Survey (SF-36) questionnaire with at least one measure at baseline (T0) and one measure at 12 weeks (T12) or 24 weeks (T24) after the end of therapy. The meta-analysis included eight studies, which involved 1,619 patients.

Results: At T12, the meta-analysis showed all items of the SF-36 questionnaire improved from the pretreatment to post-treatment period and reached statistical significance ($p < 0.05$) except for the bodily pain (mean difference: 1.16, 95%CI -0.43-2.74) and role limitations-emotional (mean difference: 4.10, 95%CI -1.32-9.52). However, after subgroup analysis (whether ribavirin was being used or not), the bodily pain domain (mean difference: 3.34, 95%CI 1.03-5.65) became statistically significant again. At T24, the results indicated that all items of the SF-36 questionnaire improved from the pretreatment to the post-treatment period and reached statistical significance ($p < 0.05$) except for the role limitations-emotional domain (mean difference: 4.50, 95%CI -2.66-11.66).

Conclusions: There is evidence indicating that DAA therapy is accompanied by an improvement in QoL. Patients receiving DAA medication have a clinically relevant improvement in most domains of the SF-36 questionnaire at T12 or T24, except for a few aspects including role limitations-emotional.

1. Introduction

The hepatitis C virus (HCV) infection is one of the most frequent causes of liver cirrhosis in the Western world, with a consequent significant social and health burden [1,2]. Extrahepatic manifestations of HCV infection include lowered quality of life (QoL) and mood disorders [3–5]. In recent years, HCV therapy has evolved from interferon-based to directly acting antiviral (DAA)-based therapy, with excellent tolerability and efficacy [6].

The Short-Form Health Survey (SF-36) questionnaire is a general health assessment tool comprised of 36 items, with each one ranging from 0 to 100 and representing eight domains of health: physical functioning, role limitations–physical, bodily pain, general health, vitality, social functioning, role limitations–emotional and mental health [7,8]. Moreover, through unique algorithms, the domains can be grouped into two summary scales: physical and mental.

At present, there are few studies on the effects of DAA on quality of life. Although some studies have used SF-36 to analyze this effect, the results vary in different SF-36 domains. It is not clear whether all dimensions of SF-36 showed improvement or just a few. In addition, most studies related have only reported the results at 12 weeks after the end of therapy (T12), and it is not clear whether the results at 24 weeks after the end of therapy (T24) are similar to those at T12. This study aimed to identify all studies evaluating the change in the QoL at baseline, 12 weeks, and 24 weeks.

Abbreviations: DAA, direct-acting antivirals; HCV, chronic hepatitis C; QoL, quality of life; SF-36, Short Form Health Survey; RCTs, controlled clinical trials

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2. Materials and methods

2.1. Data sources and retrieval

The literature review was conducted electronically through PubMed, Embase, the Cochrane Library, Wan Fang, CNKI, and Wipe databases from the database's inception to March 2021. The following keywords were used: "sofosbuvir," "simeprevir," "grazoprevir," "elbasvir," "ombitasvir," "paritaprevir," "ritonavir," "dasabuvir," "daclatasvir," "asunaprevir," "direct-acting antiviral," "DAA," "DAAs," "HCV," "hepatitis C," "Quality of Life," "QOL," "Health-Related Quality of Life," "HRQOL," "Health Status," "Status," "Health," "Level of Health," and "Health Level." All human studies were included without language restrictions.

2.2. Inclusion and exclusion criteria

The following inclusion criteria were used in the meta-analysis: (1) randomized controlled clinical trials (RCTs), cross-sectional, cohort, case-control, or observational studies that investigated the link between DAA treatment and HCV in adults; (2) studies that provided a detailed description about the quality of life scores using the SF-36 questionnaire, expressed as mean plus or minus standard deviation.

Exclusion Criteria: (1) studies involving patients with suspected or confirmed HBV, autoimmune liver disease, or drug-induced liver disease, and fatty liver disease; (2) basic medical research, review articles, or case reports; (3) studies with unclear data or inconsistent research contents.

2.3. Data analysis

Revman software 5.2 and Stata (version 15.0) were comprehensively used for data processing and analysis. The heterogeneity test was performed using I^2, with I^2 of more than 50% being considered heterogeneous. When the data were heterogeneous, the random effect model was implemented; when it was homogeneous, the fixed-effect model was utilized [9–11]. The funnel plot was used to identify publication bias [9,12,13]. Two independent reviewers (FG and HN) assessed the risk of bias according to PRISMA recommendations. Subgroup analyses were performed according to whether ribavirin was being used or not [12,13].

2.4. Register name and registration number

HE NA, 0000-0002-6654-4444.

3. Results

3.1. Search results

A total of 366 articles were initially identified from the databases. Of these, 135 articles were excluded because of data duplication and 259 articles were excluded for not meeting the criteria for inclusion. Finally, eight studies with 1,619 patients were included in the meta-analysis (Fig. 1). The basic features of these eight included studies are presented in Table 1 [14–21].

3.2. Quality assessment of the included articles

All studies were screened according to the inclusion and exclusion criteria. The present meta-analysis included five observational studies and three clinical trials. The subplots of quality evaluation are presented in **supplementary figure 1A**. The general plots of quality evaluation are presented in **supplementary figure 1B.**

3.3. Results of the meta-analysis

3.3.1. Changes in SF-36 scores from the pretreatment to 12 weeks after the end of therapy

Seven studies described the changes in SF-36 scores from the pretreatment to 12 weeks after the end of therapy [14,16-21]. Among these studies, three were conducted in America, two in Italy, one in the Netherlands, and one in multiple countries. Furthermore, 4 were observational studies and 4 were RCTs. Because some studies contain the results of different DAA treatment regiments or research participants, the data for these different subgroups will be fully extracted for analysis and distinguished in lower case letters in figures and tables [14,19,21].

The meta-analysis showed all items of the SF-36 questionnaire improved from the pretreatment to 12 weeks after the end of therapy and reached statistical significance ($p < 0.05$) except for bodily pain (mean difference: 1.16, 95%CI -0.43-2.74) and role limitations-emotional (mean difference: 4.10, 95%CI -1.32-9.52). In physical functioning, the heterogeneity test revealed significant heterogeneity ($I^2 = 53\%$). The random-effect model was used. The pooled estimate of the mean difference was 2.56 (95% CI 0.02-5.09), and the difference was statistically significant (Fig. 2A). In the limitations-physical domain, the heterogeneity test revealed significant heterogeneity ($I^2 = 59\%$), so the random effect model was used. The pooled estimate of the MD was 4.16 (95% CI 0.83-7.50), and the difference was statistically significant (Fig. 2B). Meanwhile, there was no between-study heterogeneity ($I^2 = 15\%$) in the general health domain, and the fixed-model suggested the pooled estimate of the MD was 4.73 (95% CI 3.25-6.22, Fig. 2D). The results of other aspects of SF-36 scores are shown in Fig. 2.

3.3.2. Changes in SF-36 scores from the pretreatment to 24 weeks after the end of therapy

Three studies described the changes of SF-36 scores from the pretreatment to 24 weeks after the end of therapy [14,15,21]. Among all these research, one was performed in America, one in Italy, and one in Iran. In addition, 2 were observational studies and 1 was RCT. The meta-analysis showed all items of the SF-36 questionnaire improved from the pretreatment to 24 weeks after the end of therapy and reached statistical significance ($p < 0.05$) aside from role limitations-emotional (MD: 4.50, 95%CI -2.66-11.66).

In the physical functioning domain, the heterogeneity test revealed no heterogeneity ($I^2 = 45\%$). The fixed-effect model was used. The pooled estimate of the mean difference was 5.78 (95% CI 3.97-7.60), and the difference was statistically significant (Fig. 3A). In the limitations-physical domain, there was no heterogeneity ($I^2 = 0\%$), so the fixed effect model was used. The pooled estimate of the MD was 10.68 (95% CI 8.09-13.27), and the difference was statistically significant (Fig. 3B). Moreover, there was no between-study heterogeneity ($I^2 = 49\%$) in the general health domain, and the fixed model suggested the pooled estimate of the MD was 7.66 (95% CI 5.85-9.46, Fig. 3D). The results of other aspects of SF-36 scores are shown in Fig. 3.

3.4. Subgroup analysis and publication bias

Since ribavirin may weaken the effect of DAA on SF-36 scores, we performed a subgroup analysis of results that were not statistically significant according to whether ribavirin was being used or not. First, in the domain of bodily pain (from the pretreatment to 12 weeks after the end of therapy), the pooled estimate of the MD was 3.34 (95% CI 1.03-5.65, $p < 0.05$) in DAA without ribavirin group, and the value of I^2 also gone down **(Supplementary figure 2)**. Second, in the role limitations-emotional domain (from the pretreatment to 12 weeks after the end of therapy), the pooled estimate of the MD was 4.64 (95% CI -2.58-11.87, $p > 0.05$) in DAA without ribavirin group **(Supplementary figure 3**). Third, in the role limitations-emotional

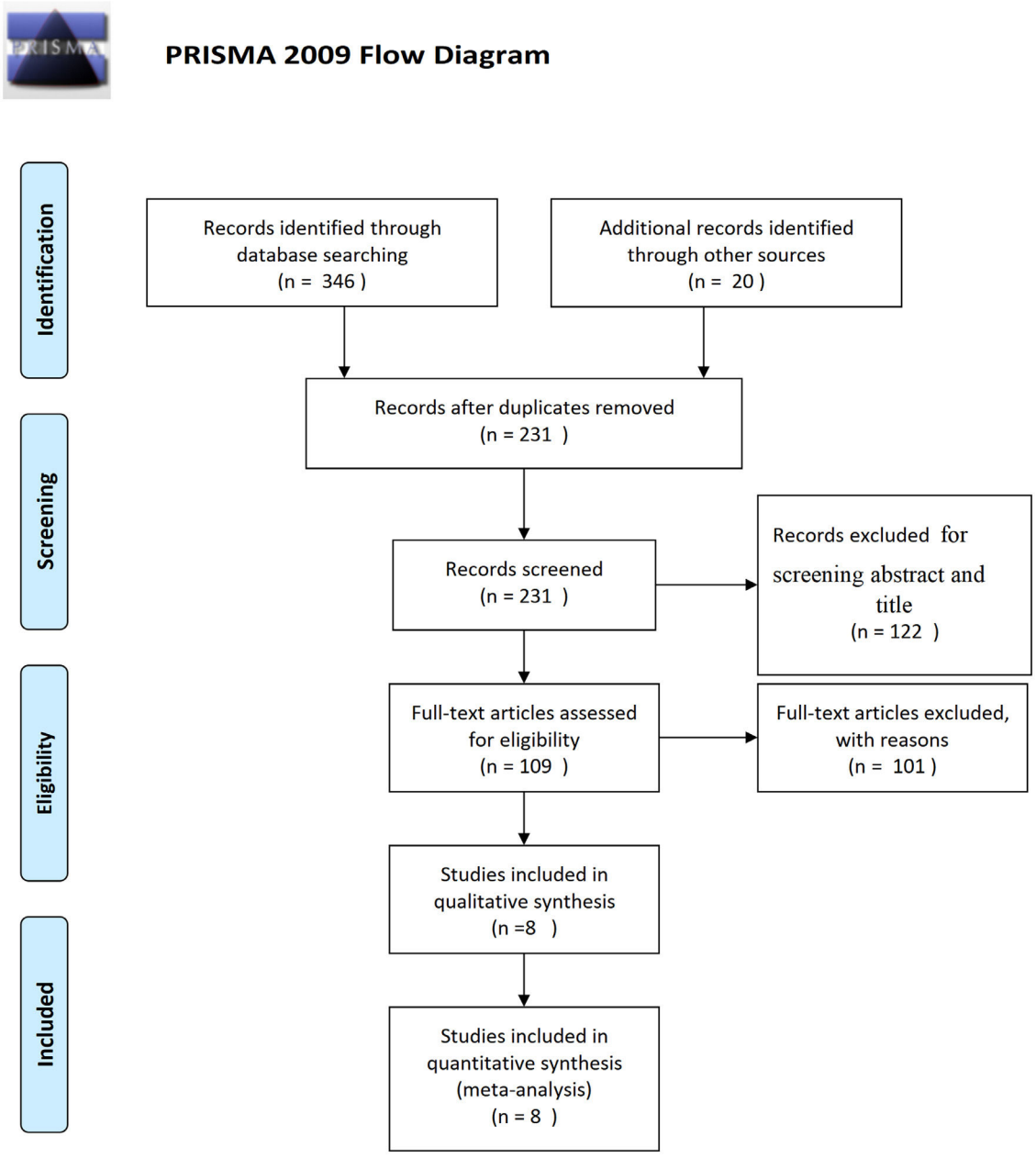

Fig. 1. PRISMA diagram of the literature search.

Table 1
Basic characteristics of the included studies.

First author	Year	Country	HCV Subgroup	Representation in forest map	Observation time after the end of the therapy (12 weeks/24weeks)	Sample	Age (years)	Male sex, *n* (%)	Cirrhosis *n* (%)	Study design
Antonella Santonicola [14]	2020	Italy	Liver transplant recipient	Antonella Santonicola_a 2020	12weeks and 24weeks	17	67.3 ± 11.4	10 (58.8)	NA	Observational study
		Italy	Kidney transplant recipient	Antonella Santonicola_b 2020	12weeks and 24weeks	11	60.7 ± 11.6	6 (54.5)	NA	Observational study
Karimi-Sari H [15]	2020	Iran	No Subgroup	Karimi-Sari H 2020	24weeks	120	41.03 ± 7.68	82(68.3)	34(28.3)	Observational study
Younossi ZM [16]	2019	America	No Subgroup	Younossi ZM 2019	12 weeks	132	42.7 ± 11.8	74(56.1)	NA	Observational study
Silvia Nardelli [17]	2019	Italy	No Subgroup	Silvia Nardelli 2019	12 weeks	39	59.8 ± 14.2	23(58.97)	NA	Observational study
Kracht PAM [18]	2018	Netherlands	No Subgroup	Kracht PAM 2018	12 weeks	68	57 (49–64)	58 (85%)	27(40.0)	Observational study
Younossi ZM [19]	2018	Multiple countries	LDV/SOF	Younossi ZM_a 2018	12weeks	384	50.5 ± 13.0	182(47.4)	58(15.1)	Clinical trial
		Multiple countries	SOF+RBV	Younossi ZM_b 2018	12weeks	475	49.2 ± 12.7	218(45.9)	73(15.4)	Clinical trial
Younossi ZM [20]	2017	America	No Subgroup	Younossi ZM 2017	12 weeks	106	54.19 ± 9.03	91(85.8)	19(17.9)	Clinical trial
Younossi ZM [21]	2016	America	Sofosbuvir and velpatasvir plus ribavirin (12 weeks)	Younossi ZM_a 2016	12weeks and 24weeks	87	57.9 ± 6.9	66(76)	87(100)	Clinical trial
			Sofosbuvir and velpatasvir (12 weeks)	Younossi ZM_b 2016	12weeks and 24weeks	90	57.7 ± 6.3	57(63)	90(100)	Clinical trial
			Sofosbuvir and velpatasvir (24 weeks)	Younossi ZM_c 2016	12weeks and 24weeks	90	57.9 ± 5.8	63(70)	90(100)	Clinical trial

HCV, hepatitis C virus; LDV, ledipasvir; SOF, sofosbuvir; RBV, ribavirin; NA, not available.

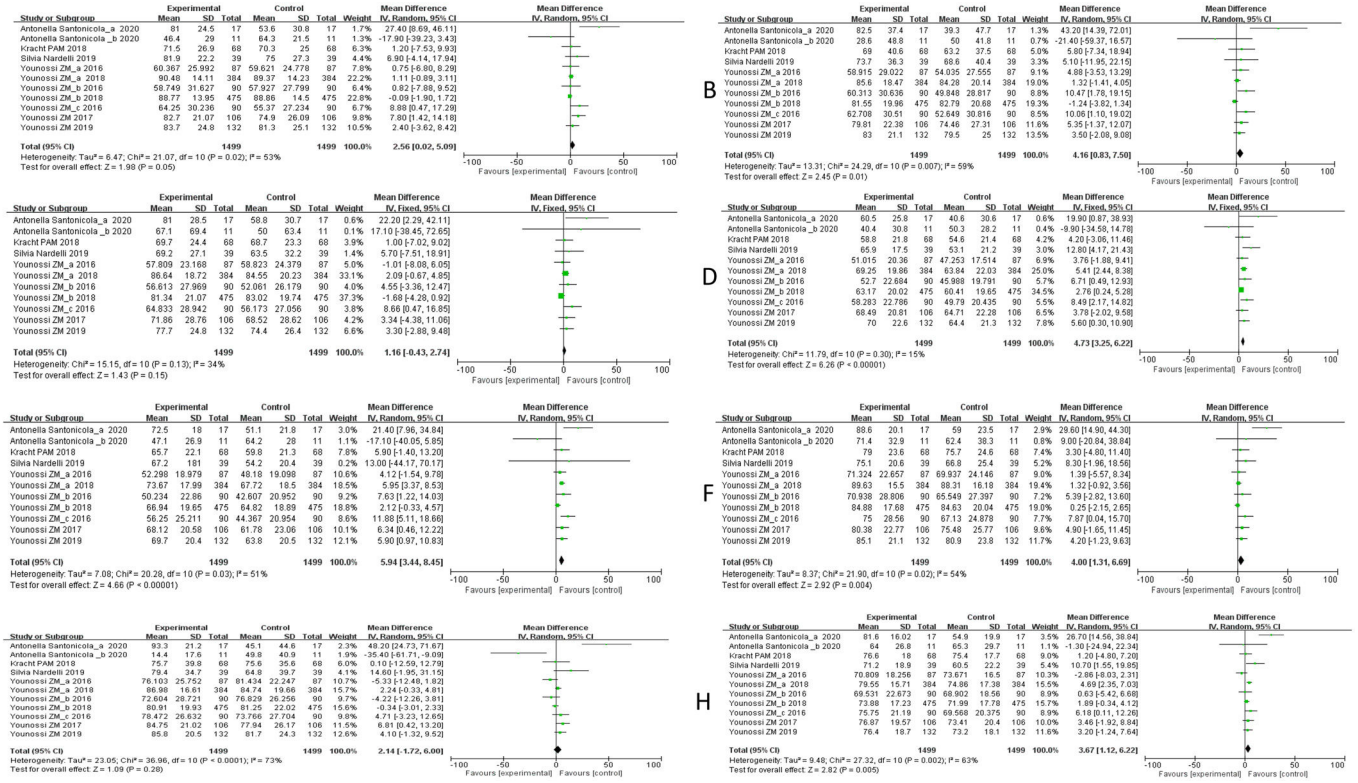

Fig. 2. Forest plot for assessing the effect of DAA on patients' QoL evaluated using SF-36 at T12.A: Forest plot for physical functioning; B: Forest plot for role limitations-physical domain; C: Forest plot for bodily pain domain; D: Forest plot for general health domain; E: Forest plot for vitality domain; F: Forest plot for the social functioning domain; G: Forest plot for role limitations-emotional domain; H: Forest plot for mental health domain.

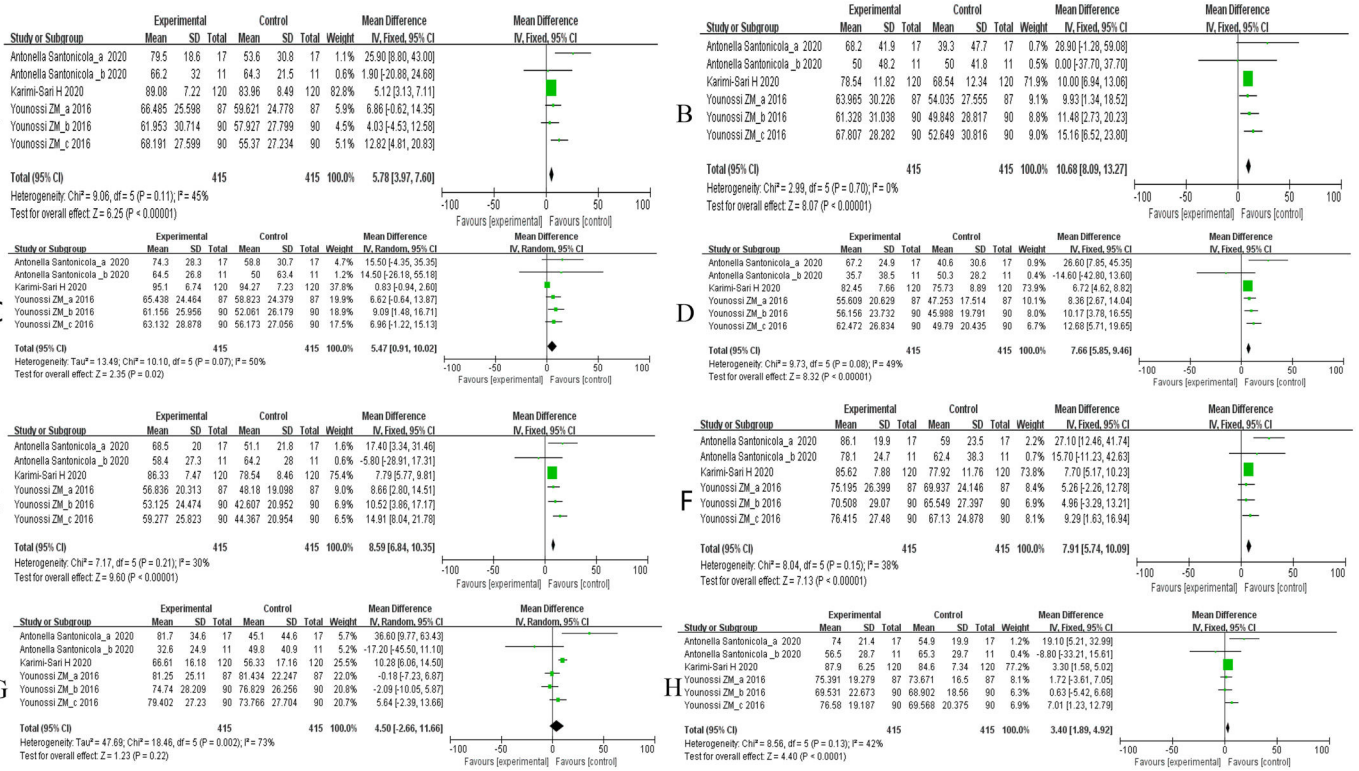

Fig. 3. Forest plot for assessing the effect of DAA on patients' QoL evaluated using SF-36 at T24.A: Forest plot for physical functioning; B: Forest plot for role limitations-physical domain; C: Forest plot for bodily pain domain; D: Forest plot for general health domain; E: Forest plot for vitality domain; F: Forest plot for the social functioning domain; G: Forest plot for role limitations-emotional domain; H: Forest plot for mental health domain.

domain (from the pretreatment to 24 weeks after the end of therapy), the pooled estimate of the MD was not statistically significant **(Supplementary figure 4).** The funnel plots were shown in **Supplementary Figure 5** and **Supplementary Figure 6**.

4. Discussion

The meta-analysis shows evidence suggesting that patients receiving DAA medication have a clinically relevant improvement in most domains of the SF-36 questionnaire at T12 or T24, except for a few aspects that may include role limitations-emotional. To our knowledge, this is the first meta-analysis of the impact of DAA on quality of life in patients with hepatitis C.

Our findings are consistent with previous research showing that DAA drugs can improve the vast majority of SF-36 domains, but not all aspects of SF-36 [17,22]. Nardelli *et al.* suggested a significant improvement of neuropsychological tests and QoL after DAAs treatment, but there was no difference in role limitation physical and bodily pain domain of SF-36 between pre-DAAs and post-DAAs [17]. Younossi *et al.* revealed that significant improvements in most SF-36 domains by post-treatment week 12 were noted, but there was no difference in physical functioning [22].

We restricted the selected studies to only those who used the Short-Form 36 (SF-36) health survey questionnaire. It is available in several languages, has demonstrated satisfactory psychometric characteristics among various groups of patients with chronic diseases, including HCV, and demonstrates good effectiveness and reliability [23–25]. Given the heterogeneity of instruments for assessing QoL, it is difficult and almost impossible to compare studies using different tools.

The studies included in the meta-analysis showed various degrees of clinical and statistical heterogeneity, although some properties make them seemingly heterogeneous, which are not associated with a reduction in QoL in patients with hepatitis C [10]. On the one hand, adopting the random effects model reduces the impairment caused by high heterogeneity in some areas [26]. On the other hand, subgroup analysis was used to avoid the effects of ribavirin. Kracht PAM *et al.* revealed that concomitant ribavirin is the only independent predictor of a transient decrease in SF-36 mental HRQL during DAA therapy [18]. With the combination of DAA and ribavirin, the final SF-36 scores were reduced, which indicated that DAA drugs did reduce the scores and its effect exceeded the effect of ribavirin; if the final SF-36 scores did not reduce, it was essential to conduct subgroup analysis according to whether ribavirin being used or not to avoid ribavirin interference.

The changes in quality of life vary in terms of improvement across SF-36 items. The SF-36 is the classic scale for quality of life, but its different dimensions reflect different aspects of quality of life. For instance, body pain refers to the effect of pain level on daily activities; the vitality dimension demonstrates the individual's subjective perception of their energy and fatigue levels, and mental health indicates an excellent ability to adapt to psychological stress [27]. In addition, some unknown factors, such as ethnic differences, may also contribute to these differences. SF-36 has been widely used in population health status detection, efficacy evaluation, health monitoring of patients with chronic diseases, and disease relative burden assessment [28]. In some previous studies, it was also mentioned that the impact of interferon therapy for HCV on quality of life in comparison with that of DAA [29]. Younossi *et al.* showed that HRQL scores decreased throughout treatment in the DAA and RBV groups versus the IFN and RBV groups. HRQL impairment was more evident with treatment regimens containing the IFN and RBV groups. Treatment-related HRQL impairment in the DAA and RBV groups was mild compared to treatment in the IFN and RBV groups and did not increase with treatment duration, and the mild decrease in HRQL was reversed four weeks after stopping treatment [29].

5. Conclusions

The current meta-analysis has some shortcomings. First, the sample size of the included articles was small and four studies were from the same author, which may affect the accuracy of the results. With the inherently low prevalence of hepatitis C and fewer studies focusing on this area, this study is a novel topic that offers a new direction of exploration to unlock the improvement and benefit of extrahepatic symptoms after the hepatitis C virus has been cleared. We have made every effort to include all possible literature. Second, the results cannot be applied to people with mental disorders since all studies were excluded from their sample patients with psychiatric disorders. Thirdly, there was heterogeneity in the findings of this study, which may have contributed to bias in the results. Future prospective studies of multicenter and larger sample sizes will be needed to validate current meta-analyses.

Author's contributions

Na He: Conceptualization; Na He, Gong Feng, Shuai Hao, Meiqi Xu: data curation, formal analysis, software, visualization, and methodology; Jing Liu, Fanjiao Kong, Zhuoxu Ren, Wenli Dou, Chengzi Yao, Tian Liang, Juan Wang: project administration and resources; Na He: supervision, and Na He, Gong Feng, and Tian Liang: writing and editing . All authors significantly contributed to the intellectual contents of this manuscript and approved its submission.

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Declarations of interest

None

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.aohep.2022.100705.

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