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



Na He^{a,*}, Gong Feng^{b,1}, Shuai Hao^b, Meiqi Xu^b, Jing Liu^c, Fanjiao Kong^c, Zhuoxu Ren^c, Wenli Dou^c, Chengzi Yao^c, Tian Liang^b, Juan Wang^c

^a The First Affiliated Hospital of Xi'an Medical University, Xi'an, China

^b Xi'an Medical University, Xi'an, China

^c Graduate School of Xi'an Medical University, Xi'an, China

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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 base-line (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.

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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].

* Corresponding author.

¹ These authors contributed equally to this study.

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.

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

E-mail address: ylhena@163.com (N. He).

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 metaanalysis (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 (I² = 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 limitationsemotional (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	$\textbf{67.3} \pm \textbf{11.4}$	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	$\textbf{57.9} \pm \textbf{6.9}$	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	$\textbf{57.9} \pm \textbf{5.8}$	63(70)	90(100)	Clinical trial

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

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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.

						1.1									Expe	erimental		LC	ntrol		Mean Difference		Mean Diffe	erence	
		Expe	rimental		C	ontrol			Mean Difference	е	Mean Difference			Study or Subaroup	Mean	SD	Total	Mean	SD T	tal Weig	ht IV. Fixed, 95% (1	IV. Fixed. 9	95% CI	
	Study or Subgroup	Mean	SD 1	Fotal	Mean	SD T	iotal V	Neight	IV, Fixed, 95%	CI	IV, Fixed, 95% Cl			Antonalla Contonicala o 2020	69.2	41.0	17	20.2	47.7	17 07	% 20 00 L1 20 50 0	21			
	Antonella Santonicola a 2020	79.5	18.6	17	53.6	30.8	17	1.1%	25.90 (8.80, 43.0	00]				Antonicila Gantonicola_a 2020	00.2	40.0		55.5	44.0	44 0.7	0 20.30 [1.20, 33.0]	2 <u>1</u>			
	Antonella Santonicola b 2020	66.2	32	11	64.3	21.5	11	0.6%	1 90 1-20 88 24 6	681				Antonella Santonicola _o 2020	50	48.2		00	41.8	11 0.5	% 0.00[-31.10, 31.11	4			
	Vorimi, Cori Ll 2020	00.00	7.22	120	20 00	0 40	120	02.0%	5121212 71	111				Karimi-Sari H 2020	78.54	11.82	120	68.54	12.34	120 71.9	% 10.00 (6.94, 13.0)	j]			
	Kallilli-Oali Fi 2020	00.00	1.22	120	03.30	0.43	120	02.070	0.12 (0.10, 7.1	11			-	Younossi ZM_a 2016	63.965	30.226	87	54.035	27.555	87 9.1	% 9.93 [1.34, 18.5]	2]	-	÷	
Α	Younossi Zm_a 2016	66.485	25.598	8/ 5	9.621	24.778	87	5.9%	6.86 (-0.62, 14.	35]			В	Younossi ZM b 2016	61.328	31.038	90	49.848	28.817	90 8.8	% 11.48 (2.73. 20.2)	31	-	-	
•••	Younossi ZM_b 2016	61.953	30.714	90 5	7.927	27.799	90	4.5%	4.03 [-4.53, 12.5	58]	-		_	Youngesi 7M c 2016	67 907	28 282	an i	52 640	20.916	an an	% 1516[652.238]	1			
	Younossi ZM_c 2016	68.191	27.599	90	55.37	27.234	90	5.1%	12.82 [4.81, 20.8	83]				T001105512/M_C 2010	01.007	20.202	50	32.043	30.010	30 3.0	/0 13.10 [0.32, 23.0	4			
	Total (95% CI)			415			415 1	100.0%	578130776	601	•			Total (95% CI)			415			115 100.0	10.68 [8.09, 13.27	1		•	
	Hatara and the Ohiz - 0.00 de - 0	0-044	12 4500	415			110	100.07	510 [557, 14	- -				Heterogeneity: Chi2 = 2.99, df = 1	5 (P = 0.70)	; F= 0%						400			
	Heterogeneity. Chir = 9.06, di = 5	(P=0.11)	1~= 45%							-11	00 -50 0 50	100		Test for overall effect 7 = 8.07 (F	P < 0.00001	D.						-100	-50 0	50	100
	Test for overall effect Z = 6.25 (P	< 0.00001									Favours (experimental) Favours (control)					<i>y</i>						Favou	rs [experimental] F	avours [control]	
		Expe	rimental		Ce	ontrol			Mean Difference	e	Mean Difference				Expe	erimental		Co	ntrol		Mean Difference		Mean Diff	ference	
	Study or Subgroup	Mean	SD	Total	Mean	SD T	otal V	Neight	IV, Random, 959	6 CI	IV, Random, 95% CI			Study or Subgroup	Mean	SD	Total	Mean	SD To	tal Weig	t IV, Fixed, 95%	CI	IV, Fixed,	95% CI	
	Antonella Santonicola_a 2020	74.3	28.3	17	58.8	30.7	17	4.7%	15.50 [-4.35, 35.	.35]				Antonella Santonicola_a 2020	67.2	24.9	17	40.6	30.6	17 0.9	% 26.60 [7.85, 45.3	35]		<u> </u>	
	Antonella Santonicola _b 2020	64.5	26.8	11	50	63.4	11	1.2%	14.50 [-26.18, 55.	.18]				Antonella Santonicola _b 2020	35.7	38.5	11	50.3	28.2	11 0.4	% -14.60 [-42.80, 13.	60]		-	
	Karimi-Sari H 2020	95.1	6.74	120	94.27	7.23	120	37.8%	0.83 [-0.94, 2.	.60]				Karimi-Sari H 2020	82.45	7.66	120	75.73	8.89 1	20 73.9	% 6.72 [4.62, 8.1	32]			
C	Younossi ZM_a 2016	00.438	24.404	8/ 5	08.823	24.379	8/	19.9%	0.02 [-0.04, 13.	.8/]	-		D	Younossi ZM_a 2016	55.609	20.629	87 .	47.253	17.514	87 10.1	% 8.36 [2.67, 14.]	14]		-	
C	Younossi ZM_c 2016	63.132	28.878	90 5	6.173	27.056	90	17.5%	6.96 [-1.22, 15	131			\mathbf{D}	Younossi ZM_0 2016	50.150	23.132	90 -	45.988	19.791	90 8.0	% 10.17 [3.78, 10.3 % 12 69 [5 71 10]	(5) (4)			
	_													1001000012m_0 2010	04.414	20.004	50	40.10	10.455	0.1	12.00 [0.11, 10.				
	Total (95% CI)			415			415 1	100.0%	5.47 [0.91, 10.	.02]	•			Total (95% CI)			415		4	15 100.0	% 7.66 [5.85, 9.4	6]		•	
	Heterogeneity: Tau ² = 13.49; Ch	*= 10.10,	if= 5 (P=	0.07);1	*= 50%					-1	100 -50 0 50	100		Heterogeneity: Chi ^a = 9.73, df =	5 (P = 0.08)); I ² = 49%	b					-100	-50 0	50	100
	rest for overall effect. Z = 2.35 (P	= 0.02)									Favours [experimental] Favours [control]			Test for overall effect: Z = 8.32 (F	P < 0.00001)						Favo	urs [experimental]	Favours [control]	
																			e 15						
		Expe	rimental		Co	ontrol			Mean Difference	9	Mean Difference			01 J 0 J	Exper	imental		Cor	itrol		Mean Difference		Mean Diff	ference	
	_Study or Subgroup	Expe Mean	rimental SD	Total	Co Mean	ontrol SD T	otal V	Weight	Mean Difference IV, Fixed, 95%	e i Cl	Mean Difference IV, Fixed, 95% Cl		J	Study or Subgroup	Exper Mean	imental SD T	otal	Cor Mean	ntrol SD To	tal Weigh	Mean Difference t IV, Fixed, 95%		Mean Diff IV, Fixed,	ference 95% Cl	
	<u>Study or Subgroup</u> Antonella Santonicola_a 2020	Expe Mean 68.5	rimental <u>SD</u> 20	Total 17	Co <u>Mean</u> 51.1	ontrol <u>SD T</u> 21.8	otal V	<u>Weight</u> 1.6%	Mean Difference IV, Fixed, 95% 17.40 (3.34, 31.4	e 6 Cl 46]	Mean Difference IV, Fixed, 95% Cl			Study or Subgroup Antonella Santonicola_a 2020	Exper Mean 86.1	imental <u>SD T</u> 19.9	iotal 17	Cor <u>Mean</u> 59	trol <u>SD To</u> 23.5	t <mark>al Weigt</mark> 17 2.2	Mean Difference IV, Fixed, 95% 6 27.10 (12.46, 41.7	CI 4]	Mean Diff IV, Fixed,	lerence 95% Cl	
	<u>Study or Subgroup</u> Antonella Santonicola_a 2020 Antonella Santonicola_b 2020	Expe Mean 68.5 58.4	rimental SD 20 27.3	<u>Total</u> 17 11	Co <u>Mean</u> 51.1 64.2	ontrol <u>SD T</u> 21.8 28	otal V 17 11	<u>Weight</u> 1.6% 0.6%	Mean Difference IV, Fixed, 95% 17.40 (3.34, 31. 5.80 (-28.91, 17.)	e <u>6 CI</u> 46] 31]	Mean Difference IV. Fixed, 95% Cl			Study or Subgroup Antonella Santonicola_a 2020 Antonella Santonicola_b 2020	Exper Mean 86.1 78.1	imental <u>SD T</u> 19.9 24.7	iotal 17 11	Cor <u>Mean</u> 59 62.4	trol <u>SD To</u> 23.5 38.3	t <mark>al Weigl</mark> 17 2.2' 11 0.7'	Mean Difference t IV. Fixed, 95% 27.10 [12.46, 41.7 5 15.70 [-11.23, 42.6	CI 4] 3]	Mean Diff IV, Fixed,	Verence 95% Cl	
	<u>Study or Subgroup</u> Antonella Santonicola_a 2020 Antonella Santonicola_b 2020 Karimi-Sari H 2020	Expe Mean 68.5 58.4 86.33	rimental SD 20 27.3 7.47	Total 17 11 120	Co <u>Mean</u> 51.1 64.2 78.54	21.8 21.8 28 8.46	otal V 17 11 120	Neight 1.6% 0.6% 75.4%	Mean Difference IV. Fixed, 95% 17.40 [3.34, 31. 5.80 [-28.91, 17. 7.79 [5.77, 9.	e <u>6 CI</u> 46] 31] 81]	Mean Difference IV. Fixed, 95% CI			Study or Subgroup Antonella Santonicola_a 2020 Antonella Santonicola_b 2020 Karimi-Sari H 2020	Exper Mean 86.1 78.1 85.62	imental <u>SD T</u> 19.9 24.7 7.88	iotal 17 11 120	Cor <u>Mean</u> 59 62.4 77.92	ntrol <u>SD To</u> 23.5 38.3 11.76 1	t <u>al Weigt</u> 17 2.2' 11 0.7' 20 73.8'	Mean Difference IV. Fixed, 95% 6 27.10 [12.46, 41.7 6 15.70 [-11.23, 42.6 6 7.70 [5.17, 10.2	CI 4] 3] 3]	Mean Diff IV, Fixed,	erence 95% Cl	
-	<u>Study or Subgroup</u> Antonella Santonicola_a 2020 Antonella Santonicola_b 2020 Karimi-Sari H 2020 Younossi ZM_a 2016	Expe Mean 68.5 58.4 86.33 56.836	rimental SD 20 27.3 7.47 20.313	Total 17 11 120 87	Co <u>Mean</u> 51.1 64.2 78.54 48.18	ontrol SD T 21.8 28 8.46 19.098	otal V 17 11 120 87	Neight 1.6% 0.6% 75.4% 9.0%	Mean Difference IV. Fixed, 95% 17.40 [3.34, 31, 5.80 [-28.91, 17, 7.79 [5.77, 9.1 8.66 [2.80, 14.3	e <u>6 CI</u> 46] 31] 81] 51]	Mean Difference IV. Fixed, 95% CI		_	Study or Subgroup Antonella Santonicola_a 2020 Antonella Santonicola_b 2020 Karimi-Sari H 2020 Younossi ZM_a 2016	Exper Mean 86.1 78.1 85.62 75.195	imental <u>SD T</u> 19.9 24.7 7.88 26.399	iotal 17 11 120 87 6	Cor <u>Mean</u> 59 62.4 77.92 9.937 2	ntrol <u>SD To</u> 23.5 38.3 11.76 1 4.146	tal Weigt 17 2.2 ⁴ 11 0.7 ⁴ 20 73.8 ⁴ 87 8.4 ⁴	Mean Difference W, Fixed, 95% 6 27.10 [12.46, 41.7 6 15.70 [-11.23, 42.6 6 7.70 [5.17, 10.2 6 5.26 [-2.26, 12.7	CI 4] 3] 3] 8]	Mean Diff IV, Fixed,	erence 95% Cl	
E	<u>Study or Subgroup</u> Antonella Santonicola_a 2020 Antonella Santonicola _b 2020 Karimi-Sari H 2020 Younossi ZM_a 2016 Younossi ZM_b 2016	Expe Mean 68.5 58.4 86.33 56.836 53.125	rimental SD 20 27.3 7.47 20.313 24.474	Total 17 11 120 87 90	Co <u>Mean</u> 51.1 64.2 78.54 48.18 (2.607	00000000000000000000000000000000000000	otal V 17 11 120 87 90	Neight 1.6% 0.6% 75.4% 9.0% 6.9%	Mean Difference <u>IV. Fixed, 95%</u> 17.40 [3.34, 31, 5.80 [-28.91, 17, 7.79 [5.77, 9, 8.66 [2.80, 14, 10.52 [3.86, 17,	e <u>i CI</u> 46] 31] 81] 51] 17]	Mean Difference N. Fixed, 95% CI		F	Study or Subgroup Antonella Santonicola_a 2020 Antonella Santonicola_b 2020 Karimi-Sari H 2020 Younossi ZM_a 2016 Younossi ZM_b 2016	Exper Mean 86.1 78.1 85.62 75.195 2 70.508	imental <u>SD T</u> 19.9 24.7 7.88 26.399 29.07	iotal 17 11 120 87 6 90 6	Cor 59 62.4 77.92 9.937 2 5.549 2	trol 23.5 38.3 11.76 1 4.146 7.397	tal Weigt 17 2.2' 11 0.7' 20 73.8' 87 8.4' 90 6.9'	Mean Difference IV. Fixed, 95% 6 27.10 [12.46, 41.7 6 15.70 [-11.23, 42.6 6 7.70 [5.17, 10.2 6 5.26 [-2.26, 12.7 6 5.26 [-3.29, 13.2	CI 4] 3] 3] 8] 1]	Mean Diff IV, Fixed,	erence 95% Cl	
E	<u>Study or Subgroup</u> Antonella Santonicola_a 2020 Antonella Santonicola_b 2020 Karimi-Sari H 2020 Younossi ZM_a 2016 Younossi ZM_c 2016	Expe Mean 68.5 58.4 86.33 56.836 53.125 59.277	rimental 20 27.3 7.47 20.313 24.474 25.823	Total 17 11 120 87 90 90	Co Mean 51.1 64.2 78.54 48.18 (2.607 (4.367	21.8 28 8.46 19.098 20.952 20.954	otal V 17 11 120 87 90 90	Neight 1.6% 0.6% 75.4% 9.0% 6.9% 6.5%	Mean Difference <u>IV, Fixed, 95%</u> 17.40 [3.34, 31. 5.80 [-28.91, 17.: 7.79 [5.77, 9.] 8.66 [2.80, 14.: 10.52 [3.86, 17.: 14.91 [8.04, 21.:	e 6 CI 46] 31] 81] 51] 17] 78]	Mean Difference N. Fixed, 95% CI		F	Study or Subgroup Antonella Santonicola_a 2020 Antonella Santonicola_b 2020 Karimi-Sari H 2020 Younossi ZM_a 2016 Younossi ZM_c 2016 Younossi ZM_c 2016	Exper Mean 86.1 78.1 85.62 75.195 70.508 76.415	imental <u>SD T</u> 19.9 24.7 7.88 26.399 29.07 27.48	17 17 11 120 87 6 90 6 90	Cor 59 62.4 77.92 9.937 2 5.549 2 67.13 2	trol 23.5 38.3 11.76 1 4.146 7.397 4.878	tal Weigt 17 2.2 ⁴ 11 0.7 ⁴ 20 73.8 ⁴ 87 8.4 ⁴ 90 6.9 ⁴ 90 8.1 ⁴	Mean Difference IV. Fixed, 95% 6 27.10 [12.46, 41.7 6 5.70 [+1.23, 42.6 6 7.70 [5.17, 10.2 6 5.26 [+2.26, 12.7 6 9.29 [1.63, 16.9	CI 4] 3] 3] 8] 1] 4]	Mean Diff IV, Fixed,	erence 95% Cl	
E	Study or Subgroup Antonella Santonicola, a 2020 Antonella Santonicola, b 2020 Karimi-Sari H 2020 Younossi ZM, a 2016 Younossi ZM, a 2016 Younossi ZM, a 2016	Expe Mean 68.5 58.4 86.33 56.836 53.125 59.277	rimental <u>SD</u> 20 27.3 7.47 20.313 24.474 25.823	Total 17 11 120 87 90 4 90	Co <u>Mean</u> 51.1 64.2 78.54 48.18 (2.607 (4.367	SD T 21.8 28 28 8.46 19.098 20.952 20.954	otal V 17 11 120 87 90 90	Neight 1.6% 0.6% 75.4% 9.0% 6.9% 6.5%	Mean Difference IV. Fixed, 95% 17.40 [3.34, 31] 5.80 [-28.91, 17.3 7.79 [5.77, 9] 8.66 [2.80, 14.3 10.52 [3.86, 17] 14.91 [8.04, 21]	e 6 CI 31] 81] 51] 17] 78]	Mean Difference N. Fixed, 95% CI		F	Study or Subgroup Antonella Santonicola_a 2020 Antonella Santonicola_b 2020 Karimi-Sant H 2020 Younossi ZM_a 2016 Younossi ZM_c 2016 Younossi ZM_c 2016	Exper Mean 86.1 78.1 85.62 75.195 70.508 76.415	imental <u>SD T</u> 19.9 24.7 7.88 26.399 29.07 27.48	17 17 11 120 87 6 90 6 90	Cor 59 62.4 77.92 9.937 2 5.549 2 67.13 2	trol <u>SD</u> To 23.5 38.3 11.76 1 4.146 7.397 4.878	tal Weigt 17 2.2' 11 0.7' 20 73.8' 87 8.4' 90 6.9' 90 8.1'	Mean Difference IV. Fixed, 95% 6 27.10 [12.46, 41.7 15.70 [+1.23, 42.6 5.26 [+2.26, 12.7 6 5.26 [+2.26, 12.7 6 9.29 [1.63, 16.9	CI 4] 3] 3] 8] 1] 4]	Mean Diff IV, Fixed,	erence 95% Cl	
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E	Study of Subgroup Antonella Santonicola, a 2020 Antonella Santonicola, b 2020 Younossi ZM, a 2016 Younossi ZM, a 2016 Total (95% CI) Heterogeneity, CI) ² = 7.17, di = 5	Expe <u>Mean</u> 68.5 58.4 86.33 56.836 53.125 59.277 i (P = 0.21)	rimental <u>SD</u> 20 27.3 7.47 20.313 24.474 25.823 [P = 30%	Total 17 11 120 87 90 4 90 4	Co <u>Mean</u> 51.1 64.2 78.54 48.18 12.607 14.367	SD T 21.8 28 8.46 19.098 20.952 20.954	otal V 17 11 120 87 90 90 415 1	Neight 1.6% 0.6% 75.4% 9.0% 6.9% 6.5% 100.0%	Mean Difference N. Fixed, 95% 17.40 [3.34, 31 5.80 [-28.91, 17 7.79 [5.77, 94 8.66 [2.80, 14 10.52 [3.86, 17 14.91 [8.04, 21 8.59 [6.84, 10.3- 8.59 [6.84, 10.3- 8.50 [6.84, 10.3- 8.59 [6.84, 10.3- 8.59 [6.84, 10.3- 8.59 [6.84, 10.3- 8.50 [6.84, 10.3- 8.59 [6.84, 10.3- 8	e <u>i CI</u> 31] 81] 51] 17] 78] → -11 -11	Mean Difference M. Fixed, 95% (1)		F	Study or Subgroup Antonella Santonicola_a 2020 Karimi-Sari H 2020 Younossi ZM_a 2016 Younossi ZM_a 2016 Younossi ZM_c 2016 Total (95% CI) Heterogeneity: Chi# = 8.04, df = 5	Exper Mean 86.1 78.1 85.62 75.195 70.508 76.415 (P = 0.15);	imental <u>SD T</u> 19.9 24.7 7.88 26.399 29.07 27.48 I [*] = 38%	International International 11 120 120 87 90 6 90 6 90 415	Cor 59 62.4 77.92 9.937 2 5.549 2 67.13 2	ntrol <u>SD</u> To 23.5 38.3 11.76 1 4.146 7.397 4.878 4	tal Weigh 17 2.2' 11 0.7' 20 73.8' 87 8.4' 90 6.9' 90 8.1' 15 100.0'	Mean Difference W, Fixed, 95% 6 27.10 [12.46, 41.7 6 27.70 [5.17, 10.2 6 7.70 [5.17, 10.2 5 2.6 [2.26, 12.7 6 9.29 [1.63, 16.9 % 7.91 [5.74, 10.0	CI 4] 3] 3] 3] 4] 4] 9]	Mean Diff	ference 95% CI 	
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E	Study or Subgroup Antonella Santonicola_a 2020 Antonella Santonicola_b 2020 Karim-SanH 2020 Younossi ZM_b 2016 Younossi ZM_b 2016 Younossi ZM_b 2016 Total (95% CD) Helerospenisty, Chi* = 7.17, df = Test for overall effect Z = 9.60 (F	Expe Mean 68.5 58.4 86.33 56.836 53.125 59.277 (P = 0.21) < 0.00001 Exp	rimental <u>SD</u> 20 27.3 7.47 20.313 24.474 25.823 (P=30%) erimenta	Total 17 11 120 87 90 4 415	Co <u>Mean</u> 51.1 64.2 78.54 48.18 12.607 14.367	21.8 28 8.46 19.098 20.952 20.954	otal V 17 11 120 87 90 90 415 1	Neight 1.6% 0.6% 75.4% 9.0% 6.9% 6.5% 100.0%	Mean Difference N. Fixed, 95% 17.40 [3.34, 31. 5.80 [2.80, 117. 7.79 [5.77, 9. 8.66 [2.80, 14. 10.52 [3.86, 17. 14.91 [8.04, 21.] 8.59 [6.84, 10.3 Mean Difference	6 CI 46] 31] 81] 51] 17] 78] 35] -11 ce	Mean Difference M. Fixed, 95% C	100	F	Study of Subgroup Antonella Santonicola, a 2020 Antonella Santonicola, b 2020 Karimi-Sari H 2020 Younossi ZM, b 2016 Younossi ZM, c 2016 Total (95% CI) Heatrogenelly: (m ² = 8, 04, df = 5 Test for overall effect Z = 7, 13 (P	Exper Mean 86.1 78.1 75.195 70.508 76.415 (P = 0.15); < 0.00001) Experime	imental <u>SD T</u> 19.9 24.7 7.88 26.399 29.07 27.48 ² = 38% Ital	Iotal 17 11 120 87 6 90 6 90 6 90 415	Con 59 62.4 77.92 9.937 2 5.549 2 67.13 2 Control	trol <u>SD</u> To 23.5 38.3 11.76 1 4.146 7.397 4.878 4	tal Weigt 17 2.2' 11 0.7' 20 73.8' 87 8.4' 90 6.9' 90 8.1' 15 100.0'	Mean Difference t IV. Fixed, 95% 6 27.10 [12.46, 41.7 1 5.70 [12.34, 24.6 7.70 [517, 10.2 5.26 [+2.26, 12.7 6 5.26 [+2.26, 12.7 6 9.29 [1.63, 16.9 % 7.91 [5.74, 10.0	C1 4] 3] 3] 8] 1] 4] 4] -100 Favo	Mean Diff	ference 95% CI	100
E	Study of Subarcop Antonella Santonicola, a 2020 Antonella Santonicola, b 2020 Karmi-Sani A 2016 Younossi ZM, a 2016 Younossi ZM, a 2016 Testa (95% C) Heterogenetity: Chill = 7, 17, df = Testa for verail effect Z = 3, 60 (F Study of Subarcop) a 2000 a 2000 a 2000	Expe Mean 68.5 58.4 86.33 56.836 53.125 59.277 (P = 0.21) < 0.00001 Exp Mean 81.7 8	rimental <u>SD</u> 20 27.3 7.47 20.313 24.474 25.823 (P = 30%) erimenta <u>SD</u> 24.6	Total 17 11 120 87 90 4 90 4 15 17 17	Co <u>Mean</u> 51.1 64.2 78.54 48.18 12.607 14.367 (4.367 (0) 00 (0) (0) (0) (0) (0) (0) (0) (0)	ontrol <u>SD T</u> 21.8 28 8.46 19.098 20.952 20.954 Control <u>SD</u> 44.6	otal V 17 11 120 87 90 90 415 1 Total	Weight 1.6% 0.6% 75.4% 9.0% 6.9% 6.5% 100.0% Weight 5.7%	Mean Difference W. Fixed, 95% 17.40 [334, 31, 5.80 [-28.91, 17.3 7.79 [5.77, 9] 8.66 [2.80, 14, 10.52 [3.86, 17.7 14.91 [8.04, 21.3 8.59 [6.84, 10.3 Mean Difference W. Random, 97 2.86,00 97, 6	e <u>i CI</u> 46] 31] 81] 51] 17] 78] 35] -11 ce 5% CI -11 ce	Mean Difference IV. Fixed, 95% CI		F	Study of Subgroup Antonella Santonicola, a 2020 Antonella Santonicola, b 2020 Yannessi ZM, a 2016 Younessi ZM, b 2016 Total (95% C) Test for overall effect Z = 7.13 (P dy of Subgroup M	Exper <u>Mean</u> 86.1 78.1 85.62 75.195 70.508 76.415 (P = 0.15); < 0.00001) Experime lean <u>S</u>	SD T 19.9 24.7 7.88 26.399 29.07 27.48 ² = 38% 1 ntal 50 Total	Total 17 11 120 87 6 90 6 90 415 Mea	Control m Solution Control m Solution Control	trol <u>SD</u> To 23.5 38.3 11.76 1 4.146 7.397 4.878 4 <u>D</u> Total	tal Weigt 17 2.2' 11 0.7' 20 73.8' 87 8.4' 90 6.9' 90 8.1' 15 100.0' Weight	Mean Difference t N. Fixed, 95% 6 27.10 [12.46, 41.7] 15.70 [-11.23, 42.8] 7.70 [5.71, 10.2] 6 5.26 [-2.26, 13.7] 6 9.29 [1.63, 16.9] % 7.91 [5.74, 10.0]	CI 41 33 31 81 11 41 41 -100 Favo	Mean Diff IV, Fixed, -50 0 0 Irss [experimenta] Mean Differen W. Fixed, 95%	Ference 95% CI	100
E	Study or Subgroup Antonella Santonicola _ 2020 Karim-San H 2020 Younossi ZM _ 2016 Younossi ZM _ 2016 Total (95% CI) Helerogeneity, Chi* = 7.17, df = 1 Test for overall effect Z = 9.60 (F Study or Subgroup Antonella Santonicola _ 2020	Expe <u>Mean</u> 68.5 58.4 86.33 56.836 53.125 59.277 (P = 0.21) < 0.00001 Exp <u>Mean</u> 81.7 32.6	rimental <u>SD</u> 20 27.3 7.47 20.313 24.474 25.823 (F = 30%) erimenta <u>SD</u> 34.6 24.9	Total 17 11 120 87 90 4 90 4 15 17 11 17 11 17 11 120 87 90 4 15 17 11 120 120 120 120 120 120 120	Co <u>Mean</u> 51.1 64.2 78.54 48.18 12.607 14.367 (C <u>Mean</u> 49.8	ontrol <u>SD 1</u> 21.8 28 8.46 19.098 20.952 20.954 Control <u>SD</u> 44.6 40.9	otal V 17 11 120 87 90 90 415 1 17 11	Weight 1.6% 0.6% 9.0% 6.9% 6.5% 100.0% Weight 5.7% 5.2%	Mean Difference M. Fixed, 95% 17.40 [3.34, 31. 5.80 [-28.91, 17. 7.79 [5.77, 9] 8.66 [2.80, 14. 10.52 [3.86, 17. 14.91 [8.04, 21.] 8.59 [6.84, 10.] Mean Differenc M. Random, 92 36.60 [9.77, 6] 36.60 [9.77, 6]	e <u>CI</u> 46] 31] 81] 51] 17] 78] ↓ -11 Ce 5% CI 13.43] 11.00	Mean Difference N. Fixed, 95% C 	100	F _ <u>stu</u>	Study of Subgroup Antonella Santonicola, a 2020 Antonella Santonicola, b 2020 Kartin-Sarl A 2020 Vounossi ZM, a 2016 Younossi ZM, c 2016 Total (95% CI) Heatrogeneity: Chi# = 0.4, df = 5 Test for overall effect Z = 7.13 (P onella Santonicola, a 2020	Exper <u>Mean</u> 86.1 78.1 85.62 70.508 76.415 (P = 0.15); < 0.00001) Experime <u>tean</u> <u>S</u> 74 21	imental SD T 19.9 24.7 7.88 26.399 29.07 27.48 * = 38% 1 Image: state s	International International 17 11 120 87 6 90 6 90 415 Meaa 54	Control mean 59 62.4 77.92 9.937 2 5.549 2 67.13 2 67.13 2 Control m S 9 19 19	ttrol <u>SD</u> To 23.5 38.3 11.76 1 4.146 7.397 4.878 4 <u>D</u> Total 9 17	tal Weigh 17 2.24 11 0.74 20 73.84 90 6.94 90 8.14 15 100.04 Weight 1.2%	Mean Difference t N. Fixed, 95% 6 27.10 [12.46, 417.3] 10 15.70 [+11.23, 42.6 6 7.70 [517, 10.2 6 5.26 [+2.2, 12.7] 4 96 [+3.29, 13.2] 6 9.29 [1.63, 16.9] % 7.91 [5.74, 10.0] Mean Difference M. Fixed, 95% [21] 10 10.[2, 12, 2.29]	CI 41 33 31 81 11 41 -100 Favo	Mean Diff IV. Fixed, -50 0 0 urs [experimental] 1 Mean Differen V. Fixed, 95%	ference 95% CI 50 Favours [control] acce	100
E	Study of Subarcom Antonella Santonicola J. 2020 Antonella Santonicola J. 2020 Karim-San H. 2020 Younossi Z.M. 2016 Younossi Z.M. 2016 Total (95% C) Heterogenety: Chir = 7.17, df = Test for overall effect Z = 9.60 C Antonella Santonicola J. 2020 Antonella Santonicola J. 2020 Antonella Santonicola J. 2020	Expe <u>Mean</u> 68.5 58.4 86.33 56.836 53.125 59.277 (P = 0.21) < 0.00001 Exp <u>Mean</u> 81.7 32.6 66.61	rimental <u>SD</u> 20 27.3 7.47 20.313 24.474 25.823 (P = 30%) erimenta <u>SD</u> 34.6 24.9 16.18	Total 17 11 120 87 90 4 90 4 15 17 4 15 1 120 11 120 11 120 11 120 120	Co Mean 51.1 64.2 78.54 48.18 12.607 14.367 14.367 C Mean 45.1 49.8 56.33	ontrol <u>SD 1</u> 21.8 28 8.46 19.098 20.952 20.954 20.954 Control <u>SD</u> 44.6 40.9 17.16	total V 17 11 120 87 90 90 415 1 17 11 120	Weight 1.6% 0.6% 9.0% 6.9% 6.5% 100.0% Weight 5.7% 5.2%	Mean Difference N. Fixed, 95% 17.40 [3:34, 31. 580 [2:80, 17. 7.79 [5:77, 91 866 [2:80, 14. 10.52 [3:86, 17. 14.91 [8:04, 21. 8.59 [6:84, 10.3 Mean Difference Y. Bandom, 92 36.60 [9:77, 6 17.20 [4:50, 1 10.28 [6:06]	3 <u>i Cl</u> 46] 31] 81] 51] 17] 78] 5% Cl 1.10] 4.501	Mean Difference IV. Fixeds, 95% CI 00 -50 0 50 Favours [experimental V. Randem, 95% CI	100	F 	Study of Subgroup Antonella Santonicola, a 2020 Antonella Santonicola, b 2020 Kanth-Sait J 2020 Younossi ZM, a 2016 Younossi ZM, c 2016 Total (95% CI) Heterogeneily: Ch ² = 8.04, df = 5 Testfor overall effect Z = 7.13 (P dy or Subgroup Mo onella Santonicola, a 2020 Mo	Exper <u>Mean</u> 86.1 78.1 85.62 75.195 70.508 76.415 (P = 0.15); < 0.00001) Experime lean <u>S</u> 74 21 56.5 28 74 21	imental SD T 19.9 24.7 7.88 26.399 29.07 27.48 27.48 27.48 I* = 38% 1 1 35.0 Ital 50 Total 36.0 25 10.2 10.2 10.2	iotal 17 11 120 87 6 90 6 90 415 Meaa 54 65	Control Mean 59 62.4 77.92 9.937 2 5.549 2 67.13 2 0 0 19 3 29 29 29 29 29 29 29 29 29 29	trol <u>SD</u> To 23.5 38.3 11.76 1 4.146 7.397 4.878 4 <u>D</u> Total 9 17 7 11 4 12	tal Weigh 17 2.24 11 0.74 20 73.84 90 6.94 90 8.14 15 100.00 Weight 1.2% 0.4% - 2.26	Mean Difference IV. Fixed, 95% 0 27.10 [12.46, 11.3, 42.6 5 7.10 [12.46, 11.3, 42.6 6 7.70 [51.7, 10.2, 42.6 5 25.26 [2.26, 12.7 6 9.29 [1.63, 16.9 % 7.91 [5.74, 10.0 Mean Difference M. Fased, 95% c1.1 19.10 [5.21, 32.99] 806 [3.22, 1, 5.61]	CI 4] 3] 3] 8] 1] 4] -100 Favo	Mean Diff IV, Fixed, -50 0 0 urs [experimental] 1 Mean Differen IV, Fixed, 95%	ference 95% C1 50 Favours [control] nce	100
E	Study or Subgroup Antonella Santonicola_02020 Karim-San H 2020 Younossi ZM_2016 Younossi ZM_2016 Younossi ZM_2016 Tetal (95% C) Helerogeneik_Chi# = 7.17, df = f Test for overall effect Z = 8.00 (F Study or Subgroup Antonella Santonicola_02020 Antonella Santonicola_02020 Karimi-Sant 2020	Expe <u>Mean</u> 68.5 58.4 86.33 56.836 53.125 59.277 (P = 0.21) < 0.00001 Exp <u>Mean</u> 81.7 32.6 66.61 81.25	rimental <u>SD</u> 20 27.3 7.47 20.313 24.474 25.823 (F = 30%) erimenta <u>SD</u> 34.6 24.9 16.18 25.11	Total 17 11 120 87 90 4 90 4 15 17 4 15 17 11 120 87 90 4 15 11 120 87 90 4 15 11 120 87 90 4 15 15 11 120 15 15 15 15 15 15 15 15 15 15	Co Mean 51.1 64.2 78.54 48.18 12.607 14.367 14.367 56.33 81.434	ontrol <u>SD T</u> 21.8 28 8.46 19.098 20.952 20.954 20.954 20.954 Control <u>SD</u> 44.6 40.9 17.16 22.247	total V 17 11 120 87 90 90 415 1 17 11 120 87 87	Neight 1.6% 0.6% 9.0% 6.9% 6.5% 100.0% Weight 5.7% 5.2% 25.5% 22.0%	Mean Difference <u>N. Fixed, 95%</u> 17.40 [3.34, 31. 5.80 [2.80, 1.77] 7.79 [5.77, 9] 8.66 [2.80, 143] 10.52 [3.86, 17] 14.91 [8.04, 21] 8.59 [6.84, 10.3] Mean Different <u>N. Random, 95</u> 36.60 [9.77, 6] -17.20 [4.55.0] 10.22 [6.06, 1] -0.18 [4.73]	3 <u>i</u> <u>Cl</u> 46] 31] 51] 17] 78] 55% <u>Cl</u> -11 -11 Ce 5% <u>Cl</u> -11 -11 4.60] 4.60]	Mean Difference M. Fixed, 595-00	f	F 	Study of Subgroup Antonella Santonicola, a 2020 Antonella Santonicola, b 2020 Karimi-Sari H 2020 Vounossi ZM, a 2016 Younossi ZM, c 2016 Total (95% Ch) Hetrogenelly, Ch) Hetrogenelly, Ch) norsila Santonicola, a 2020 Imimi Sari Horizon Moreilia Santonicola, a 2020 Imimi Sari Horizon	Exper Mean 86.1 78.1 85.62 70.508 70.508 76.415 (P = 0.15); < 0.00001) Experime lean <u>5</u> 74 21 56.5 28 87.9 6.3 391 19.2	sp T 19.9 24.7 7.88 29.07 27.48 29.07 27.48 29.07 19.9 27.48 19.0 12.0 19.0 12.1 24.7 12.1 20.07 12.1 27.48 12.1 10.1 12.1 10.2 12.0 7.9 87	(otal 17 11 120 87 6 90 415 415 Mea 54 65 4 7367 54 7367 54 54 54 54 54 54 54 55 55 55	Control mean 59 62.4 77.92 9.937 2 5.549 2 67.13 2 67.13 2 0 19 3 29 6 7.3 19 3 29 19 3 29 19 19 19 19 19 19 19 19 19 1	ttrol <u>SD</u> To 23.5 38.3 11.76 1 4.146 7.397 4.878 4 <u>D</u> Total 9 17 7 11 14 120 5 87 5 87	tal Weight 17 2.2' 11 0.7' 20 73.8' 87 8.4' 90 6.9' 90 8.1' 15 100.0' Weight 1.2% 0.4% - 77.2% 8.1%	Mean Difference t N. Kixed, 95% 6 27.10 [12.46, 41.7] 16.70 [+11.23, 42.6 6 6 7.70 [5.17, 10.2 6 2.66 [-2.63, 12.7] 7 6.96 [-2.63, 22.6] 7 6 9.29 [1.63, 16.9] % 7.91 [5.74, 10.0] Wean Difference M. Fixed, 955 C1 19.10 [5.21, 32.99] 3.00 [1.56, 10.21]	CI 4] 3] 3] 8] 4] 4] -100 - Favo	Mean Diff N, Fixed, -50 0 urs [experimental] I Mean Differen V. Fixed, 95%	Favours [control]	100
E	Study of Subarcom Antonella Santonicola_a 2020 Antonella Santonicola_b 2020 (Karim-Sant 2020 Younossi 2M_a 2016 Younossi 2M_a 2016 Total (95% C) Heterogeneity: Chi# = 7.17, df = Test for overall effect Z = 9.80 (C Antonella Santonicola_a 2020 Antonella Santonicola_a 2020 Antonella Santonicola_a 2020 Antonella Santonicola_a 2020 Younossi 2M_a 2016	Expe <u>Mean</u> 68.5 58.4 86.33 56.836 53.125 59.277 (P = 0.21) < 0.00001 Exp <u>Mean</u> 81.7 32.6 66.61 81.25 74.74	rimental <u>SD</u> 20 27.3 7.47 20.313 24.474 25.823 (F = 30%) erimenta <u>SD</u> 34.6 24.9 16.18 25.11 28.209	17 17 11 120 87 90 4 415 4 15 17 11 120 87 90 90	Co <u>Mean</u> 51.1 64.2 78.54 48.18 12.607 14.367 45.1 45.1 45.1 56.33 81.434 76.829	ontrol <u>SD T</u> 21.8 28 8.46 19.098 20.952 20.954 20.954 20.954 Control <u>SD</u> 44.6 40.9 17.16 22.247 26.256	otal V 17 11 120 87 90 90 415 1 17 11 120 87 90	Veight 1.6% 0.6% 9.0% 6.9% 6.5% 100.0% Weight 5.7% 5.2% 22.0% 20.8%	Mean Difference M. Fixed, 95% 17.40 [3:34, 31. 580 [289,11,77. 779 [5:77,91] 866 [280,144, 21. 14.91 [8.04, 21. 8.59 [6.84, 10.5 Mean Difference M. Random, 95 38.60 [9.77, 61. 10.28 [6.06, 1. -0.18 [F.7.3], -2.09 [1-105.]	a <u>6</u> CI 46] 31] 51] 17] 78] 55% CI -11 (3.43) 1.10] (4.50] 1.450] 5.87]	Mean Difference IV. Fixed, 95% CI	f	F <u>Stu</u> Antı Kar H You	Study of Subtroup Antonella Santonicola _ 2 2020 Antonella Santonicola _ 2 2020 Xanto-sella Santonicola _ 2 2020 Younessi ZM _ 2 0016 Younessi ZM _ 2 0016 Total (95% CI) Heterogenelly: Ch ² = 8 04, df = 5 Test for overall effect Z = 7.13 (P Moneilla Santonicola _ 2 2020 mossi ZM _ 2 0016 mossi ZM _ 2 0016 mossi ZM _ 2 0016	Exper Mean 86.1 78.1 78.62 75.195 70.508 76.415 (P = 0.15); < 0.00001)	sp T 19.9 24.7 7.88 26.399 29.07 27.48 /*= 38% 1 I*= 38% 1 125 120 77 9.87 73 90	(otal 17 11 120 87 6 90 6 90 415 415 Mea 54 65 84 73.67 68.90	Control m 59 62.4 77.92 9.937 2 5.549 2 67.13 2 67.13 2 67.13 2 67.13 2 8 7.13 2 9 .3 29 .3 29 .4 29 .3 29 .3 29 .5 29	ttrol <u>SD</u> To 23.5 38.3 11.76 1 4.146 7.397 4.878 4 <u>D</u> Total 9 17 7 11 14 120 5 87 16 90	tal Weight 17 2.2' 11 0.7' 20 73.8' 87 8.4' 90 6.9' 90 8.1' 15 100.0' Weight 1.2% 0.4% - 77.2% 8.1% 6.3%	Mean Difference IM, Fixed, 95% 27.10 [12.46, 94.7] 5 15.70 [-11.23, 42.6 6 7.70 [12.246, 94.7] 5 5.26 [-2.26, 12.7] 6 4.96 [-3.29, 13.2] 6 9.29 [1.63, 16.9] % 7.91 [5.74, 10.0] Mean Difference M.K.66, 95% C1 19.10 [5.71, 32.99] 8.80 [-3.32, 11.561] 3.30 [1.58, 5.02] 17.27 [-3.61, 7.05] 0.63 [-5.24, 6.68]	CI 4] 3] 3] 8] 1] 4] 4] -100 -100 Favo	Mean Diff N, Fixed, -50 0 0 urs [experimental] Mean Differen M. Fixed, 555	Ference 95% CI	100
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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, sub-group 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. Treatmentrelated 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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