REVIEW

Effects of sustained viral response on lipid in Hepatitis C: a systematic review and metaanalysis

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Abstract

Background Direct-acting Antiviral Agents (DAAs) influence serum lipids of patients with Hepatitis C virus (HCV). This paper presents an analysis of the relevant literature to investigate the effects of DAAs in treating hepatitis C to achieve a sustained viral response (SVR) on lipid parameters.

Methods PubMed, Web of science, Embase and Central databases were searched, with a deadline of September 2023. Studies on the effects of sustained viral response on lipid parameters after DAAs treatment for hepatitis C were selected. The required information was extracted from the included studies, and then the Stata 12.0 was used to analyze the data quantitatively.

Results Of 32 studies, the results showed that total cholesterol (TC) levels increased from the end of treatment (WMD = 20.144, 95%CI = 3.404, 36.884, P = 0.018) to one year after treatment (WMD = 24.900, 95%CI = 13.669, 36.131, 10.000)P < 0.001). From the end of treatment (WMD = 17.728, 95%Cl = 4.375, 31.082, P = 0.009) to one year after treatment (WMD = 18.528, 95%Cl = 7.622, 29.433, P < 0.001), the levels of low-density lipoprotein (LDL) were also increased. High-density lipoprotein (HDL) levels were elevated from 4 weeks after treatment (WMD = 6.665, 95%Cl = 3.906,9.424, P < 0.001) to 24 weeks after treatment (WMD = 3.159,95% CI = 0.176, 6.142, P = 0.038). Triglyceride (TG) levels showed no significant change after the treatment.

Conclusions Hepatitis C patients who achieved SVR on DAAs showed the increase of lipid levels and the improvement of hepatic inflammation indicators AST and ALT. This may provide evidence-based medical evidence for

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Keywords Direct-acting Antiviral agents, Hepatitis C, Sustained viral response, Lipid, Meta-analysis

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the follow-up and monitoring of blood lipids and hyperlipidemia treatment.







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Background

Hepatitis C virus (HCV) is a plus-strand RNA virus whose infection is mainly confined to liver cells and is an important cause of cirrhosis, liver cancer, and liver transplantation [1]. In 2019, the World Health Organization reported that about 58 million people worldwide are infected with chronic hepatitis C [2].

Studies have found that infection with HCV can affect lipid and lipoprotein metabolism levels in the body [3]. The typical presentation is enhanced lipid production and decreased lipoprotein secretion, which accelerates the process of atherosclerosis and liver steatosis [4, 5]. Moreover, clinical studies have found that the prevalence of liver steatosis in CHC patients is 40–86%, which is much higher than 20–50% of other chronic liver disease patients without hcv infection [6, 7]. Therefore treatment of HCV may be crucial in regulating the lipid metabolic disorders it causes. Sustained viral response (SVR) is defined as the disappearance of HCV RNA in plasma at 12 or 24 weeks after completion of treatment [8]. Before the advent of direct-acting antiviral drugs (DAAs), hepatitis C was mainly based on interferon (IFN), but its SVR rate was only about 50%, with serious side effects [9]. Recently developed DAAs are emerging as a new branch of standard HCV therapy that can significantly improve treatment outcomes [3]. Scott A McDonald et al. [10].

Patients with decompensated cirrhosis who received no interferon prior to the advent of DAA were compared and analysed with those who received no interferon DAA in the era of DAA. Patients with decompensated cirrhosis in the DAA era have a significantly lower risk of liver-related death.

In addition, Tanaka et al. [11]. found that DAA administration after hepatectomy could improve liver function in patients with HCC, which may prolong postoperative survival. Moreover, the study also found that DAA can adversely affect lipid profiles by eradicating HCV, which increases the risk of cardiovascular disease development. However, SVR can ultimately improve overall cardiovascular mortality by eliminating many other harmful effects of HCV [12].Therefore, it is particularly important to further understand the influence of DAAs treatment on the lipid profile of patients who achieved a sustained viral response to HCV.

Currently, there are many domestic and foreign studies on the relationship between DAAs treatment and lipid parameters in HCV patients. But the results are not identical. In 2018, Kawagishi N et al. [13] successfully eliminated HCV with interferon-free DAAs reducing low-density lipoprotein cholesterol (LDL-C) levels in patients with higher baseline values and in patients with hepatic steatosis and dyslipidemia in SVR24. Increased LDL-C levels are accompanied by increased sdLDL-C (Small and dense LDL-C) levels.

Kawagishi N et al. [13] successfully eliminated HCV with interferon-free DAAs in 2018, reducing low-density lipoprotein cholesterol (LDL-C) levels in SVR24 patients with higher baseline values and mid-hepatic steatosis and dyslipidemia. Elevated LDL-C levels are accompanied by increased levels of sdLDL-C (small, dense LDL-C).

However, Pedersen et al. [14] found that successful DAA treatment could increase LDL and Highdensity lipoprotein (HDL). In contrast, Triglyceride (TG) levels were reduced after treatment. This metaanalysis further explored the effect of DAA treatment on lipid levels from the perspective of a comprehensive assessment of the effect of persistent hepatitis C virus response on lipid parameters. In particular, the duration of lipid changes and the changes of lipid in patients with different genotypes or different SVR. So as to provide a reference for clinicians to individualized treatment.

Materials and methods

This meta-analysis followed the PRISMA guidelines [15]. The search strategies and inclusion and exclusion criteria were registered with PROSPERO (PROSPERO-CRD 42,020,180,793).

Search strategies

The Medical Subject Heading terms and keywords used in the search process mainly included: "Hepatitis C," "Hepacivirus," "Sofosbuvir," "DAA," "Lipid Met abolism," "Cholesterol," "Triglyceride," "Cholesterol, HDL," "Cholesterol, LDL," and "Apolipoproteins." The databases searched included PubMed, Central, Embase, Web of Science. The search period was September 2023.

Inclusion and exclusion criteria

The inclusion criteria:(1) The subjects of studies were patients with HCV; (2) studies on HCV patients who received DAA therapy; (3) availability of relevant lipid data before and after treatment; (4) studies in which persistent viral responses in HCV patients were clear and (5) prospective or retrospective studies. The exclusion criteria: (1) the study population was co-infected with HIV/HCV; (2) interferon was included in the treatment regimen; (3) text type: reviews, editorials, letters, case reports, personal newsletters, pre-prints and abstracts. Literature screening and data extraction were conducted independently by two researchers. First, primary literature retrieval was carried out, and then the literature retrieved at the primary level was screened according to pre-set criteria. When two researchers had different opinions, they discussed and settled together to reach a unified standard.

Quality evaluation of literature evidence

The Newcastle Ottawa Scale (NOS) was used to assess study quality. We assessed the quality of the evidence for each relevant study. (The total score is 9 points. 7-9points: High-quality; 4–6 points Moderate-quality; 0–3 points Low-quality)

Data extraction

Two independent researchers conducted the data extraction according to the formulated unified and standardized data tables. Relevant experts were invited to review these controversial issues. Data were extracted based on the following parameters: First author, Publication year, Country or region, Study type, Age, Percentage of males, DAAs protocol, Genotype, Sample size, SVR status, Baseline lipid parameters, and Lipid parameters at and after treatment (12 weeks, 24 weeks or one year). Mean \pm standard deviation (SD) or median (interquartile spacing) was used to express age parameters and sex information was expressed as the percentage of males in each group.

The primary outcome

(1) Changes in TG, total cholesterol (TC), LDL and HDL levels after DAAs treatment (at the end treatment, 4w after treatment, 12w after treatment, 24w after treatment, and one year after treatment) in patients who achieved sustained viral response compared with baseline; (2) Changes in lipids of patients with different SVR (SVR12 or SVR24) or different genotypes; (3) Changes of indicators of hepatic inflammation (AST and ALT) before and after treatments; (4) In part of the study, changes of lipids in patients with cirrhosis and non-cirrhosis were analyzed.

Statistical analysis

The software used in this study was Stata 12.0, and WMD values and the corresponding 95% confidence interval (CI) were used to measure and evaluate the association strength. Heterogeneity between studies was tested using the Q-test statistics and I² values, and the I² value was used to measure heterogeneity. Heterogeneity test I² < 50% indicated no significant heterogeneity. Therefore, WMD was calculated using a fixed effects model. If heterogeneity was present, a random-effects model was selected. The Z statistic was used to test the combined WMD values. Differences with statistical significance was defined as P < 0.05. Egger's linear regression method was used to evaluate publication bias. Sensitivity analysis was performed by eliminating individual studies individually.

Results

Search results

A total of 1159 qualified studies were preliminarily retrieved according to the set retrieval formula, and 933 articles were retrieved that might be included in the study excluding 226 duplicate studies. After reading titles and abstracts, 848 irrelevant papers were excluded. 85 studies were excluded after reading the full text. Finally, 29 eligible papers were included (Fig. 1).

Basic features of the included studies

Eleven studies were prospective studies, 13 were retrospective studies, one was retro-prospective study and seven types of studies were not mentioned in this metaanalysis; patients achieved SVR12 in twenty five studies and SVR24 in seven studies; one study reported changes in lipids in patients with significant and non-significant liver fibrosis, and three studies reported changes in lipids in patients with cirrhosis and non-cirrhosis. The research areas include Asia (India, Japan, Tai Wan), South America (Brazil), Europe (Italy, Spain, Germany), Africa (Egypt), North America (America, Canada) and Oceania (New Zealand). The basic characteristics are summarized in Table 1.

Quality evaluation of literature evidence

NOS scores were performed on the 32 included studies, and the results showed that the scores of all studies were no less than six, indicating that the 32 studies were of.

medium and high quality. (Supplementary Table 1).

Change in TC after antiviral therapy

Figure 2 shows the changes in total cholesterol levels in patients who achieved a sustained viral response after DAAs treatment. Results show that the TC level increased at the end of treatment (WMD = 18.905, 95%CI = 3.495, 34.314, P = 0.016), 4 weeks after completion of treatment (WMD = 20.901, 95%CI = 15.335, 26.468, P < 0.001), 12 weeks (WMD = 23.255, 95%CI = 9.414, 37.096, *P* = 0.001), 24 weeks (WMD = 19.635, 95% CI = 16.353, 22.917, P < 0.001) and one year (WMD = 24.900, 95% CI = 13.669, 36.131, P < 0.001) after treatment compared with that before the treatment. Because of the high heterogeneity of the study, sensitivity analyses were performed and the results were found to be stable. And there was no significant publication bias, so a random-effects model was appropriate for statistical analysis.

Change in LDL after antiviral therapy

Figure 3 shows the changes in LDL levels in HCV patients after DAAs treatment ended. Compared with before of treatment, serum LDL levels increased from



Fig. 1 Flow diagram of study selection

the end of treatment (WMD = 16.88, 95%CI = 4.564, 29.195,P = 0.007) to 1 year after treatment (WMD = 17.372, 95%CI = 10.152, 24.592, P < 0.001). Heterogeneity was the same as that for TC, and there was no significant publication bias.

Change in HDL after antiviral therapy

As Fig. 4 shows, the levels of HDL from 4 weeks after treatment (WMD = 6.665, 95%CI = 3.906-9.424, P < 0.001) to 24 weeks after treatment (WMD = 3.159, 95%CI = 0.176-6.142, P = 0.038) were elevated compared with that before the treatment. However, at the end of treatment (WMD=-0.030, 95%CI = -1.595-1.536, P = 0.970) and one year after the end of treatment (WMD = 0.136, 95%CI = -2.929-3.200, P = 0.931), the changes of HDL levels were not significant.

ication bias, so a trim and fill analysis was carried out. Before the trim-and-fill test, the heterogeneity test was Q = 381.642, P < 0.001, and the random effect model was adopted. The combined effect size result was 2.397, 95% CI = 1.308–3.485, and the heterogeneity test after the trim-and-fill Q = 718.837, P < 0.001. The combined effect size was 0.844 (with 95% CI = 0.270–2.644). The results were not reversed before and after trim-and-fill analysis, indicating that the results were relatively robust.

Change in TG after antiviral therapy

Figure 5 shows the changes of TG in patients before and after treatment, and there was no statistically significant at the end of treatment (WMD = 3.403, 95%CI =-15.915-22.721, P = 0.730), 12 weeks after completion of treatment (WMD = 7.616, 95%CI =-12.893, 28.1248, P = 0.467), 24 weeks after completion of treatment (WMD= -0.772,95% CI=-2.170,0.626, P = 0.279).

Table 1 Characteristics of Studies and patients								
First author	Country/	Study design	Antiviral	Genotype	Weeks of	SVR(W)	Numbe	
Year	Region		regimens		treatment			
Jain [16] 2018	India	prospective	SOF/DCV	G3	12	SVR12	47	

Tabl

First author Year	Country/ Region	Study design	Antiviral regimens	Genotype	Weeks of treatment	SVR(W)	Number	Age (Years)	Males
Jain [<mark>16</mark>] 2018	India	prospective	SOF/DCV	G3	12	SVR12	47	38±13	60%
lchikawa [17] 2019	Japan	retrospective	DCV/ASV	G1b	24	SVR24	38	70.92 ± 11.02	36%
lchikawa [18] 2019	Japan	retrospective	Multiple DAA regimens	Multiple genotypes	12/24	SVR12	48	70.1 ± 11.08	42%
Cheng [19] 2018	Tai wan	prospective	SOF/DCV	G2	12	SVR12	31	65.0 ± 13.2	28.10%
Cheng [<mark>20</mark>] 2019	Tai wan	prospective	Multiple DAA regimens	Multiple genotypes	12/24	SVR12	102 AF 76	66.0 ± 10.7 68.0 ± 9.3	33.30% 32.90%
							NAF 26	60.3 ± 12.6	34.6%
Gilmar [<mark>21</mark>] 2018	Brazil	retrospective	Multiple DAA regimens	Multiple genotypes	12/24	SVR12	43	60.5 ± 9.5	27.90%
Inoue [22]	Japan	NA	DCV/ASV	G1b	24	SVR24	69	68.3 + 10.5	38.80%
2018				G1b	12	SV/R24	8/	61.4 ± 13.3	13 50%
				615	12	CV/D2.4	45	62.0 + 15.2	22.00/
			SOF/RBV	G2	12	SVR24	45	62.0 ± 15.3	32.60%
Gitto [23] 2018	Italy	NA	Multiple DAA regimens	Multiple genotypes	12/24	SVR24	93	64±12	60.20%
El Sagheer [24] 2018	Egypt	NA	SIM/SOF	G4	12	SVR12	79	47 ± 12	58.80%
Chida [<mark>25</mark>] 2018	America	retrospective	DCV/ASV	G1b	24	SVR12	67	71±9	40.00%
Andrade [26] 2018	Brazil	retro-prospective	Multiple DAA regimens	Multiple genotypes	12	SVR12	95	56 ± 9	70%
Juanbeltz [27] 2017	Spain	retrospective	Multiple DAA regimens	Multiple genotypes	12/16/24	SVR12	212	53.6 ± 9.3	71.80%
Endo [<mark>28</mark>]	Japan	NA	DCV/ASV	G1b	24	SVR12	121	68.4 ± 11.8	48.80%
2017			SOF/LDV	G1b	24	SVR12	132	66.7 ± 13.1	37.10%
Pedersen [14] 2016	America	prospective	SOF/RBV	G2	12/24	SVR12	58 C 33 NC 25	55.5 ± 12.1	61.20%
			SOF/RBV	G3	12/24	SVR12	31 C 14 NC 17	54.6 ± 10.8	64.50%
Shimizu [<mark>29</mark>] 2018	Japan	NA	Multiple DAA regimens	G1/G2	12/24	SVR12	70	66 (59–73)	41.40%
Beig [<mark>30]</mark> 2018	New Zealand	retrospective	Multiple DAA regimens	NA	NA	SVR12	35	NA	NA
Sun [<mark>31</mark>] 2017	Tai wan	NA	GZR/EBV or SOF/LDV	G1	12	SVR12	22	60 (39 ~ 83)	50%
Doyle [<mark>32</mark>] 2019	Canada	NA	PrOD	G1a/G1b	12	SVR12	23	54 ± 11.6	71%
Muñoz.H [<mark>33</mark>] 2020	NA	prospective	Multiple DAA regimens	Multiple genotypes	12	SVR12	109	53.6 ± 10.8	69.70%
Sangineto [34] 2021	Italy	retrospective	Multiple DAA regimens	NA	NA	SVR24	95	67.1 ± 0.8	50.60%
Inomata [35] 2022	Japan	retrospective	SOF/LDV	G1b	12	SVR12	22	60.5 (55–69)	50%
Graf [<mark>5</mark>] 2020	Germany	retrospective	Multiple DAA regimens	Multiple genotypes	12	SVR24	45	51.7 ± 14.1	47.80%
Chen [<mark>36</mark>] 2020	Tai wan	prospective	Multiple DAA regimens	Multiple genotypes	12/24	SVR12	102	65.9 ± 9.9	32.40%

Table 1 (continued)

First author Year	Country/ Region	Study design	Antiviral regimens	Genotype	Weeks of treatment	SVR(W)	Number	Age (Years)	Males
lossa [37] 2021	Italy	retrospective	Multiple DAA regimens	Multiple genotypes	12	SVR24	47 C 31	66 (62–71)	42.90%
Eletreby [38] 2021	Egypt	prospective	SOF/DAC ± RBV	Multiple genotypes	12/24	SVR12	NC 18 264	51.73 ± 10.24	89.20%
Nevola [39] 2020	Italy	prospective	Multiple DAA regimens	Multiple genotypes	8–24	SVR24	243	68 (62–74)	46.90%
Joshita [<mark>40</mark>] 2021	Japan	retrospective	Multiple DAA regimens	Multiple genotypes	8/12/24	SVR12	231	70 (63–76)	42.00%
Abdoa [41] 2020	Egypt	retrospective	SOF/DCV	NA	12/24	SVR12	98 C 32 NC 66	51.54 ± 6.91	44.90%
Hino [<mark>42</mark>] 2021	NA	retrospective	Multiple DAA regimens	Multiple genotypes	12	SVR12	67	70.0 (62–77)	40.30%
Anca [<mark>43</mark>] 2023	Italy	retrospective	Multiple DAA regimens	NA	12	SVR12	132	61.17 ± 9.11	35.6%
Ahmed [44] 2023	Egypt.	retrospective	Multiple DAA regimens	NA	12	SVR12	100	50.99 ± 8.75	100%
Diego [<mark>45</mark>] 2023	Spain	retrospective	Multiple DAA regimens	Multiple genotypes	8/12	SVR12	83	55 (49–63)	49.4%

NA, not available; AF, Advanced fibrosis; NAF, Non-advanced fibrosis; C, Cirrhotics; NC, Non-cirrhotics;

SOF: Sofosbuvir; DCV: Daclatasvir; ASV: Asunaprevir; LDV: Ledipasvir;

LDV: Ledipasvir;RBV: Ribavirin;SIM: Simeprevir;GZR: Grazoprevir;

EBV: Elbasvir; PrOD: paritaprevir/ritonavir/ombitasvir/dasabuvir;DAC: Daclatasvir

Subgroup analysis was performed according to different SVR

Supplementary Figs. 1 and 2 show the changes in TC and LDL levels in patients with different SVR. The results showed that in patients who achieved SVR12 and SVR24, the serum TC levels (SVR12: WMD = 22.743, 95%CI = 11.064, 34.423, P < 0.001; SVR24: WMD = 19.401, 95% CI = 17.335,21.468, P < 0.001;) and LDL levels (SVR12: WMD = 19.612, 95%CI = 12.253, 26.971, P < 0.001; SVR24: WMD = 17.017, 95% CI = 13.735,20.298, P < 0.001;) increased after treatment. There was no publication bias.

Subgroup analysis was performed according to different genotypes

Supplementary Fig. 3 shows the changes in TC and LDL levels in the patients with different genotypes. The results showed that serum TC and LDL levels of patients with the G1b, G1, G2, and G3 genotypes increased after treatment, with no publication bias. (Supplementary Table 2).

Change of AST and ALT

Seven studies reported changes in AST levels before and after treatment. AST levels decreased after treatment compared to before treatment (WMD=-27.339, 95%CI = -35.294, -19.385, P < 0.001), as shown in Supplementary Fig. 4. Ten studies reported changes in ALT before and after treatment, and ALT levels also decreased after treatment (WMD=-40.820, 95%CI = -49.872, -31.767, P < 0.001), as shown in Supplementary Fig. 5. There was a publication bias in both cases. After two iterations, there were no missing articles, and the research results were relatively reliable.

Change in lipids in patients with Cirrhosis and noncirrhosis

Three studies reported changes in lipid levels in patients with cirrhosis and non-cirrhosis. Pooled analysis showed that TC in cirrhosis and non-cirrhosis patients (cirrhosis: WMD = 13.824, 95% CI = 7.310, 20.337, P < 0.001; non-cirrhosis: WMD = 17.139, 95%CI = 10.601,23.676, P < 0.001) and LDL (cirrhosis: WMD = 8.498, 95%CI = 3.474, 13.522, P = 0.001;non-cirrhosis: WMD = 17.702, 95%CI = 12.349, 23.67623.054, P < 0.001) after treatment was increased compared with that before treatment, as shown in Supplementary Figs. 6 and 7. TG and HDL levels were not statistically significant in either population, and there was no significant heterogeneity or publication bias.

Discussion

This study aims to show lipid changes in HCV patients who achieve SVR after DAA treatment and persistent changes in blood lipid levels within 1 year after DAA treatment.

ETO EI Sagheer (2018) Graf (2020) Gilmar (2018) Juanbeltz (2017) Pedersen (2016) Munoz.H (2020) Eletreby (2021) Nevola (2020) Anca (2020) Subtotal (I-squared = 98.4%, p = 0.000) W Chida (2018) Endo (2017) Endo (2017) Subtotal (I-squared = 11.9%, p = 0.321) W Chida (2018) Doyle (2019) Jain (2019) Cheng (2019) Graf (2020) Gilmar (2018) Marca (2023) Subtotal (I-squared = 11.9%, p = 0.321) W Chida (2018) Doyle (2019) Graf (2020) Cheng (2019) Graf (2020) Cheng (2019) Graf (2020) Cheng (2019) Graf (2020) Cheng (2017) Shimizu (2018) Sun (2018) Inomet (2021) Cheng (2021) Anca (2022) Chen (2021) Nuce (2018) Inoue (2018) Inoue (2018) Inoue (2019) Inoue (2018) Inoue (2018) Sangineto (2021) Ossa (2021) Cheng (16.90 (6.38, 27.42) 17.50 (1.84, 33.16) -0.40 (-15.28, 14.48) 12.00 (4.95, 19.05)	1.95
w Chida (2018) Endo (2017) Subtotal (I-squared = 11.9%, p = 0.321) 12w Chida (2018) Doyle (2019) Cheng (2019) Cheng (2019) Graf (2020) Gilmar (2018) Juanbeltz (2017) Endo (2017) Shimizu (2018) Sun (2018) Sun (2018) Sun (2018) Inomata (2022) Chen (2021) Eletreby (2021) Abdoa (2020) Ichikawa (2019) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2021) Arca (2023) Ahmed (2023) Subtotal (I-squared = 98.3%, p = 0.000) 24w Graf (2020) Doyle (2019) Inoue (2018) Inoue (2018) Sangineto (2021) Iossa (2021)	0.10 (-12.41, 12.61) 16.10 (-2.05, 34.25) 19.10 (8.71, 29.49) 79.95 (75.21, 84.69) 18.00 (12.41, 23.59) 19.00 (17.47, 20.53) 6.55 (-1.76, 14.86) 18.90 (3.49, 34.31)	1.77 1.80 2.05 1.89 1.67 1.96 2.09 2.08 2.13 2.02 21.41
12w Chida (2018) Doyle (2019) Jain (2019) Cheng (2019) Cheng (2019) Graf (2020) Gilmar (2018) Juanbeltz (2017) Endo (2017) Endo (2017) Shimizu (2018) Juanbeltz (2017) Endo (2017) Endo (2017) Endo (2017) Shimizu (2018) Inomata (2022) Chen (2021) Abdoa (2020) Ichikawa (2019) Inoue (2018) Sangineto (2021) Iossa (2021)	22.00 (11.33, 32.67) 25.07 (16.63, 33.51) 16.01 (7.58, 24.44) 20.90 (15.33, 26.47)	1.95 2.01 2.01 5.98
24w Graf (2020) Doyle (2019) Ichikawa (2019) Inoue (2018) Inoue (2018) Inoue (2018) Gitto (2018) Sangineto (2021) Iossa (2021)	$\begin{array}{c} 25.00 & (14.50, 35.50) \\ 31.00 & (15.28, 46.72) \\ 25.50 & (13.52, 37.48) \\ 16.00 & (-3.61, 35.61) \\ 17.60 & (9.03, 26.17) \\ 18.70 & (0.79, 36.61) \\ 18.30 & (2.34, 34.26) \\ 17.00 & (5.65, 28.35) \\ 23.00 & (16.24, 29.76) \\ 23.13 & (14.30, 31.96) \\ 14.47 & (6.67, 22.27) \\ 13.80 & (-1.79, 29.39) \\ 17.30 & (-1.28, 35.88) \\ 21.00 & (16.12, 25.88) \\ 16.90 & (8.43, 25.37) \\ 119.67 & (114.49, 124.85) \\ 17.80 & (10.89, 24.71) \\ 38.10 & (20.79, 55.41) \\ 25.30 & (14.04, 36.56) \\ 13.30 & (3.91, 22.69) \\ 14.80 & (-0.22, 29.82) \\ 23.00 & (18.26, 27.74) \\ 15.33 & (6.34, 24.32) \\ -9.92 & (-20.15, 0.31) \\ 23.26 & (9.41, 37.10) \\ \end{array}$	1.95 1.77 1.91 1.62 2.01 1.68 1.76 2.06 2.03 1.77 1.66 2.09 2.05 1.71 1.93 1.99 1.80 2.00 1.96 45.86
Nevola (2020) Subtotal (I-squared = 76.0%, p = 0.000)	24.60 (7.23, 41.97) 27.10 (11.38, 42.82) 29.30 (13.88, 44.72) 33.70 (21.70, 45.70) 13.40 (4.08, 22.72) 12.60 (-1.43, 26.63) 20.00 (10.08, 29.92) 19.90 (18.71, 21.09) 21.00 (16.06, 25.94) 15.00 (13.46, 16.54) 19.63 (16.35, 22.92)	1.70 1.77 1.78 1.90 1.99 1.83 1.97 2.13 2.09 2.13 19.30
Ivear Gilmar (2018) Beig (2018) Munoz.H (2020) Chen (2021) Subtotal (I-squared = 70.4%, p = 0.017)	31.60 (14.81, 48.39) 42.60 (26.25, 58.95) 16.40 (6.58, 26.22) 16.40 (7.75, 25.05) 24.90 (13.67, 36.13)	1.73 1.74 1.97 2.01 7.45
Overall (I-squared = 97.7%, p = 0.000) NOTE: Weights are from random effects analysis	22.21 (17.15, 27.26)	100.00

Fig. 2 Forest plot of serum TC changes after treatment at each time point

$ \begin{array}{c} \text{ETO} \\ \text{ES} \text{Sapherr} (2018) \\ \text{Gard} (2028) \\ \text{Ginard} (2018) \\ \text{Jamchetz} (2017) \\ \text{Parkins (2017)} \\ \text{Find} (2018) \\ \text{Chida} (2018) \\ \text{Call (1-squared = 96.7\%, p = 0.000)} \\ \text{Wark (Call (2018))} \\ \text{Chida} (2018) \\ \text{Call (2018)} \\ \text{Call (2019)} \\ \text{Chida} (2018) \\ \text{Call (2019)} \\ \text{Chida} (2018) \\ \text{Call (2017)} \\ \text{Find} (2017) \\ \text{Find} (2017) \\ \text{Find} (2017) \\ \text{Chida} (2018) \\ \text{Call (2018)} \\ \text{Call (2017)} \\ \text{Endo (2017)} \\ \text{Chida} (2018) \\ \text{Call (2018)} \\ \text{Call (2019)} \\ \text{Call (2021)} \\ \text{Call (2019)} \\ \text{Call (2021)} \\ \text{Call (2018)} \\ \text{Call (2021)} \\ \text{Call (2018)} \\ \text{Call (2018)} \\ \text{Call (2019)} \\ \text{Call (2018)} \\ \text{Call (2019)} \\ \text{Call (2018)} \\ \text{Call (2019)} \\ \text{Call (2019)} \\ \text{Call (2018)} \\ \text{Call (2019)} \\ \text{Call (2018)} \\ \text{Call (2018)} \\ \text{Call (2019)} \\ \text{Call (2018)} \\ \text{Call (2018)} \\ \text{Call (2019)} \\ \text{Call (1-squared = 97.6\%, p = 0.000)} \\ Call (1-squared = 97.6\%$	Study ID	WMD (95% CI)	% Weig
 Li segneret (vol19) Grid (2020) Grid (2020) Pedersen (2016) Pedersen (2016) Pedersen (2016) Pedersen (2016) Nerola (2020) Stobial (-Equard = 98.0%, p = 0.000) Aw Chida (2018) Endo (2017) Stobial (-Equard = 98.0%, p = 0.000) Aw Chida (2018) Endo (2017) Stobial (-Equard = 98.0%, p = 0.000) Aw Chida (2018) Endo (2017) Stobial (-Equard = 66.7%, p = 0.0054) Tay (-Ching (2018) Chida (2018) Endo (2017) Chida (2018) Chida (2018) Endo (2017) Chida (2018) Chida (2019) Junobelic (2017) Endo (2017) Chida (2018) Chida (2013) Chida (2014) Chida (2015) Chida (2015) <lichida (2016)<="" li=""> Chida (2016) Chida (2016)<</lichida>			
Cried (2020) 17.00 (2.97, 21.30) 1.99 Decision (2016) 1.00 (1.14, 20.13) 1.99 Pedersen (2016) 1.00 (1.14, 20.13) 1.91 Minoz L (2021) 1.81 (1.15, 23.19) 1.84 Electerby (2021) 1.83 (1.68, 68, 66) 2.01 Icosea (2021) 1.81 (1.15, 23.19) 1.83 Subtotal (I-squared = 98.0%, p = 0.000) 3.83 (1.02, 21.72) 1.83 Aw Chida (2018) 1.81 (1.15, 25.15) 1.83 Doyle (2019) 1.81 (1.15, 25.15) 1.83 1.83 Chida (2018) 2.10 (1.16, 9.0.31) 1.83 Doyle (2019) 2.10 (1.69, 3.38, 85.5) 1.53 Simbotal (I-squared = 65.7%, p = 0.054) 1.80 (8.16, 27.74) 1.81 Lamobic (2017) 1.82 (1.16, 2.33, 82.5) 1.53 Simbota (2019) 2.10 (1.73, 3.86.5) 1.53 Gimar (2018) 2.10 (1.69, 3.31, 1.55 1.55 Simbota (2017) 1.80 (8.8, 2.16.6) 1.52 Simbota (2017) 1.80 (8.8, 2.16.6) 1.55 Simbota (2017) 1.80 (8.8, 2.16.6) 1.55 Simbota (2017) 1.80 (8.8, 2.16.6)	El Sagheer (2018)	21.40 (10.85, 31.95)	1.77
Glimar (2018) 1.90 (-11.14, 14.34, 19.19) 1.94 Peaceser (2016) 1.90 (-11.14, 14.34, 19.19) 1.95 Minocet (2020) 21.20 (11.50, 30.90) 1.41 Eletreby (2021) 1.98 (4.50, 30.90) 1.41 Dessa (2021) 1.98 (4.50, 30.90) 1.41 Nexola (2020) 1.80 (6.16, 27.84) 1.81 Nexola (2020) 8.00 (6.66, 9.34) 2.07 Area (2023) 1.80 (6.16, 27.84) 1.81 Endo (2017) 1.81 (5.21.15) 1.93 Endo (2017) 1.81 (5.21.15) 1.93 Subtolal (I-squared = 98.0%, p = 0.0054) 1.80 (6.16, 27.84) 1.81 Jan (2019) 2.100 (11.69, 30.31) 1.83 Cheig (2019) 2.100 (11.62, 3.31, 77) 1.67 Jannebet (2017) 1.81 (5.11, 7.26, 15) 1.93 Endo (2017) 1.82 (6.02, 27, 71) 1.85 Endo (2017) 1.84 (4.82, 72, 23) 1.99 Simucu (2018) 1.90 (4.11, 4.44, 4.12) 1.65 Juanobet (2017) 1.81 (5.11, 7.26, 65) 1.50 Endo (2017) 1.81 (5.11, 7.26, 75) 1.83 Simucu (2018)	Graf (2020)	17.00 (2.97, 31.03)	1.59
Junchett (2017) Pedersen (2016) Pedersen (2016) Pedersen (2016) Pedersen (2017) Lossa (2021) Nevola (2020) Ava Ava Ava Ava Ava Ava Ava Ava	Gilmar (2018)	1.90 (-11.14, 14.94)	1.64
Pedersen (2016) Pedersen (2016) Munoz H (2020) Heredsvan (2017) Ender (2017) Chan (2017) Chan (2018) Chan (2018) Chan (2019) Chan (2011) Endo (2011) Endo (2011) Endo (2011) Endo (2011) Endo (2011) Endo (2011) Endo (2011) Chan (2012) Chan (2021) Chan (2021) C	Juanbeltz (2017)	14.00 (7.81, 20.19)	1.96
Pederaen (2016) Munoz H (2020) Nervala (2020) Nervala (2020) Nervala (2020) Avervala (2021) Avervala (2021) Avervala (2021) Avervala (2021) Avervala (2021) Avervala (2022) Chene (2021) Avervala (2022) Chene (2021) Avervala (2022) Avervala (2023) Subtradi (I-squared = 97.6%, p = 0.000) Yeard Gimer (2018) Avervala (2021) Avervala (2021) Avervala (2022) Avervala (2023) Subtradi (I-squared = 97.6%, p = 0.000) Yeard Gimer (2018) Avervala (2021) Avervala (2022) Avervala (2021) Avervala (2022) Avervala (2021) Avervala (2022) Avervala (2023) Subtradi (I-squared = 97.6%, p = 0.000) NDTE: Weichts are from random effects analysis	Pedersen (2016)	0.70 (-11.00, 12.40)	1.71
Muncz H (2020) lestereby (2021) lestereby (2021) lestereby (2021) lestereby (2021) lestereby (2021) lestereby (2020) Arra (2023) Subtral (L-squared = 98.0%, p = 0.000) Arr Chiai (2018) Endo (2017) Endo (2017) Subtral (L-squared = 65.7%, p = 0.054) "12w Chiai (2018) Dayle (2018) Chiai (2018) Endo (2017) Chiai (2018) Endo (2017) Chiai (2018) Chiai (2018) Endo (2017) Endo (2017) Chiai (2018) Endo (2017) Endo (2017) Chiai (2018) Endo (2017) Endo (2018) Endo (2017) Endo (2018) Endo (2017) Endo (2018) Endo (2017) Endo (2018) Endo (2018) En	Pedersen (2016)	12,50 (-4,19, 29,19)	1.45
Electedy (2021) Nevola (2020) Avar (2023) Subtolal (I-squared = 98.0%, p = 0.000) Av Chida (2018) Endo (2017) Endo (2018) Subtolal (I-squared = 97.6%, p = 0.000) Typer Gimar (2018) Subtolal (I-squared = 97.6%, p = 0.000) Typer Gimar (2018) Subtolal (I-squared = 97.0%, p = 0.000) Typer Figuide (I-squared = 97.0%, p = 0.000)	Munoz H (2020)	21.20 (11.50, 30.90)	1.81
Tabes (2021) 14.00 (9 98; 1620) 200 Array (2023) 8.00 (666; 9.34) 2.07 Array (2023) 8.00 (666; 9.34) 2.07 Subtotal (I-squared = 98.0%, p = 0.000) 18.00 (816, 27.24) 18.01 (816, 27.24) Array (2019) 18.01 (816, 27.24) 18.01 (816, 27.24) 18.01 (816, 27.24) Table (2017) 18.00 (816, 27.24) 18.01 (816, 27.24) 18.01 (816, 27.24) Table (2019) 18.10 (2019) 18.10 (2019, 22.24.15) 18.00 (816, 27.24) 18.00 (816, 27.24) Table (2019) 21.00 (11.69, 30.31) 18.35 (11.17, 26.55) 19.00 (81.69, 27.21) 18.00 (81.69, 27.21) Table (2019) 18.10 (20.23, 23.17) 14.00 (82.24.215) 18.00 (81.69, 27.21) 18.00 (82.24.215) 18.00 (82.24.215) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (81.69, 27.21) 18.00 (82.81, 27.21) 18.00 (82.81, 27.21) 18.00 (82.81, 27.21) 18.00 (82.81, 27.21) 18.00 (82.81, 27.21) 18.00 (82.81, 27.21) 18.00 (82.81, 27.21) </td <td>Eletreby (2021)</td> <td>63 92 (59 18 68 66)</td> <td>2 01</td>	Eletreby (2021)	6 3 92 (59 18 68 66)	2 01
Naroda (2020) 8.00 (d 666, 9.24) 2.07 Arca (2023) 8.00 (d 666, 9.24) 1.86 Subtotal (I-squared = 98.0%, p = 0.000) 8.00 (d 666, 9.24) 1.86 Arca (2023) 1.80 (d 17) 1.81 (f 11.15, 25.15) 1.39 Endo (2017) 1.81 (f 11.15, 25.15) 1.39 1.37 1.00 (r 2, 33, 38.85) 1.55 Subtotal (I-squared = 65.7%, p = 0.054) 1.80 (d 17, 33, 38.85) 1.55 1.53 2.21 (o 17, 23, 38.85) 1.56 Cheng (2019) Cheng (2019) 2.17 (d 17, 23, 38.85) 1.55 1.46 1.46 (1 0.42, 28.17) 1.56 Graf (2020) Graf (2020) 1.80 (d 11.17, 26.66) 1.80 1.55 Graf (2021) Janhade (2016) 1.20 (d 2.8, 27.72) 1.58 Graf (2021) Janhade (2017) 1.80 (d 11.17, 26.66) 1.80 (d 11.17, 26.66) 1.80 Enterbay (2021) Janhade (2017) 1.80 (d 1.17, 26.66) 1.80 1.81 (f 1.17, 26.66) 1.80 Janhade (2016) 1.80 (d 1.17, 26.66) 1.80 1.80 (d 1.17, 26.66) 1.80 Janhade (2018) 1.81 (d 1.17,			2.03
Arca (2023) Arca (2023) Subtal (I-squared = 98.0%, p = 0.000) Arca (2023) Arca (2023) Arca (2023) Arca (2023) Arca (2023) Arca (2023) Arca (2023) Subtal (I-squared = 97.0%, p = 0.004) T2W Chida (2016) Endo (2017) Shrinzu (2018) Shrinzu (2018) Inoue (Nevola (2020)	8 00 (6 66 9 34)	2.00
Subtorial (L-squared = 96.0%, p = 0.000) 4w Chida (2018) Endo (2017) Endo (2017) Endo (2017) Endo (2017) Endo (2017) Endo (2017) Endo (2018) Subtorial (L-squared = 65.7%, p = 0.054) Law Cheng (2018) Endo (2019) Cheng (2019) Endo (2019) Endo (2019) Endo (2017) Endo (2017) Endo (2019) Endo (2017) Endo (2017) Endo (2019) Endo (2017) Endo (2018) Endo (2017) Endo (2018) Endo (2019) Endo (2018) Endo (2019) Endo (2010) Endo (2010)	Anca (2023)	8 36 (-0.26, 16.98)	1.86
Awr 1000 (1+0.2120) 1000 (1+0.2120) Chida (2018) 18.00 (8.16, 227.84) 1.81 Endo (2017) 18.15 (11.15, 25.15, 19.39 7.31 (0.67, 13.395) 1.65 Subtotal (1-squared = 65.7%, p = 0.054) 14.12 (6.52, 21.72) 5.89 Tay 21.00 (11.69, 30.31) 1.83 Doyle (2019) 20.70 (28.3, 33.71) 107 Chida (2016) 20.70 (28.3, 33.71) 107 Chida (2017) 18.10 (0.83, 35.37) 1.42 Chida (2016) 20.70 (28.3, 33.71) 107 Chida (2017) 18.10 (0.83, 35.77) 1.82 Simiar (2018) 14.12 (6.52, 27.71) 1.88 Chida (2017) 18.84 (1.01, 12.86 1.92 Shmizu (2018) 10.38 (4.00, 15.76) 1.96 Shmizu (2018) 10.38 (4.00, 15.76) 1.96 Inoue (2018) 10.38 (4.00, 15.76) 1.96 Inoue (2018) 10.38 (4.00, 15.76) 1.96 Inoue (2018) 10.98 (1.17, 22.5, 18.45) 2.00 Inoue (2018) 10.98 (1.12, 22, 18.45) 2.00 Inoue (2018) 10.90 (1.46, 31.56) 1.96 Inoue (20	Subtotal (Lequared = 98.0%, p = 0.000)	16 88 (4 56, 29 20)	10.00
Am 18.00 (8:16, 27.84) 1.81 Endo (2017) 1.81 11.51 (5:11, 52.515) 1.93 Subtotal (I-squared = 65.7%, p = 0.054) 7.31 (0.67, 13.25) 1.55 12w 1.12 (0.67, 13.25) 1.93 1.93 1.93 Dayle (2019) 2.100 (11.69, 30.31) 1.83 2.31 (0.73, 33.85) 1.50 12w (Cheng (2019) 2.100 (11.69, 30.31) 1.83 2.31 (0.73, 33.85) 1.50 12a (2018) 2.100 (11.69, 30.31) 1.83 2.31 (0.73, 33.85) 1.50 12a (2018) 1.84 (11.17, 28.61) 1.86 1.84 (11.17, 28.61) 1.86 12a (2018) 1.84 (11.17, 28.61) 1.86 1.84 (11.17, 28.61) 1.98 12a (2018) 1.84 (11.17, 28.61) 1.98 1.98 (11.17, 28.61) 1.98 12a (2018) 1.84 (11.16, 1.82) 1.98 (11.17, 28.61) 1.98 12a (2018) 1.98 (11.17, 28.61) 1.98 1.98 (11.17, 28.61) 1.98 12a (2018) 1.98 (11.17, 28.61) 1.98 1.98 (11.17, 28.61) 1.98 11noue (2018) 1.100 (13.83 (10.		10.00 (4.00, 20.20)	10.00
Chida (2018) Endo (2017) Subtotal (I-squared = 65.7%, p = 0.054) 12w Chida (2018) Dayle (2019) Jam (2019) Cheng (2012) Cheng (2021) Cheng (2023) Subtotal (I-squared = 97.6%, p = 0.000) Typer Subtotal (I-squared = 97.6%, p = 0.000) Typer Subtotal (I-squared = 97.6%, p = 0.000) NOTE: Weichts are from random effects analysis	4w		
Endo (2017) Endo (2017) Subtola (I-squared = 65.7%, p = 0.054) T2w Childs (2018) Dayle (2019) Lam (2019) Cheng (2019) Cheng (2019) Cheng (2019) Cheng (2019) Endo (2017) Endo (2018) Endo (2018) Endo (2019) Endo (2018) Endo (2019) Endo (2018) Endo	Chida (2018)	18.00 (8.16, 27.84)	1.81
Endo (2017) Endo (2018) Doyle (2019) Jam (2019) Cheng (2019) Jan (2019) Cheng (2019) Jan (2019) Cheng (2019) Cheng (2019) Cheng (2019) Cheng (2019) Cheng (2019) Cheng (2019) Cheng (2019) Cheng (2019) Endo (2017) Endo (2011) Johinau (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Endo (2021) Cheffact (2022) Subtotal (I-squared = 97.6%, p = 0.000) Year Grif (2022) Subtotal (I-squared = 97.6%, p = 0.000) NOTE: Weights are from random effects analysis Endo (2023) Note: (2019) Cheffact (2021) Cheffact (2021) Cheffact (2022) Cheffact (2022) Cheffact (2022) Cheffact (2022) Cheffact (2022) Cheffact (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Cheffact (2022) Cheffact (2022) Cheffact (2022) Cheffact (2021) Cheffact (2018) Cheffact (2018) Cheffact (2018) Cheffact (2021) Cheffact (2018) Cheffact (2021) Cheffact (2021) C	Endo (2017)	18.15 (11.15, 25.15)	1.93
Subtoral (I-squared = 65.7%, p = 0.054) 12w Chida (2018) Doyle (2019) 3an (2019) Cheng (2019) Graf (2020) Simira (2018) Andrade (2018) Andrade (2018) Cheng (2019) Graf (2020) Shimizu (2017) Endo (2017) Shimizu (2018) Andrade (2018) Cheng (2017) Shimizu (2018) Cheng (2021) Cheng (2022) Cheng (2023) Cheng (2023) Cheng (2021) Cheng (2021) Cheng (2023) Subtoral (I-squared = 97.6%, p = 0.000) Year Graf (2020) Subtoral (I-squared = 77.0%, p = 0.000) NOTE: Weights are from random effects analysis	Endo (2017)	7.31 (0.67, 13.95)	1.95
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	Subtotal (I-squared = 65.7%, p = 0.054)	14.12 (6.52, 21.72)	5.69
$ \frac{12w}{13m} (2018) \\ Dxyle (2019) \\ Jain (2019) \\ Cheng (2019) \\ Cheng (2019) \\ Graf (2020) \\ Gimar (2018) \\ Andrade (2018) \\ Jannobetz (2017) \\ Endo (2017) \\ The Calculation (2017) \\ Dismark (2018) \\ Jannobetz (2017) \\ Shimizu (2018) \\ Shimizu (2018) \\ Shimizu (2018) \\ Shimizu (2018) \\ Danobetz (2022) \\ Cheng (2021) \\ Ched (2017) \\ Endo (2017) \\ Shimizu (2018) \\ Inowata (2022) \\ Cheng (2021) \\ Jannobetz (2021) \\ Jannobetz (2021) \\ Jandota (2022) \\ Chen (2021) \\ Jashimizu (2018) \\ Inowata (2022) \\ Thimo (2021) \\ Inowata (2022) \\ Thimo (2018) \\ Inowata (2023) \\ Janouet (2018) \\ Inowata (2019) \\ Inowata (2019) \\ Inowata (2018) \\ Inowata (2019) \\ Inowata (2020) \\ Subtotal (I-squared = 97.6\%, p = 0.000) \\ $		· · · · · · · · · · · · · · · · · · ·	
Chick (2018) Doyle (2019) Jain (2019) Cheng (2018) Landrade (2017) Endo (2011) Abdina (2022) Abdoa (2020) Hino (2021) Chen (2021)	12w		
Uoyle (2019) 23.10 (219) Cheng (2019) 20.70 (8.23.33.17) 1.46 Cheng (2019) 16.20 (8.25.24.15) 1.89 Graf (2020) 11.460 (10.42.81.6) 1.82 Gimar (2018) 14.460 (10.42.81.6) 1.82 Andrade (2013) 12.20 (8.25.27.11) 1.89 Endo (2017) 18.40 (10.42.81.6) 1.82 Endo (2017) 18.40 (10.42.81.6) 1.90 Shimizu (2018) 17.40 (10.7.67, 23.13.81 1.90 Juanbeltz (2022) 12.80 (8.89, 19.29) 1.99 Chen (2021) 12.80 (8.89, 19.29) 1.99 Joshinizu (2018) 1.92 1.93 1.90 Inoue (2018) 1.90 2.90 (14.48, 41.92) 1.91 Inoue (2018) 1.92 1.93 1.92 Inoue (2018) 1.94 2.94 (44.41.76) 1.48 Inoue (2018) 1.94 (1.92.21) 2.90 1.93 (45.42, 27.25)	Chida (2018)	21.00 (11.69, 30.31)	1.83
Jain (2019) Cheng (2019) Cheng (2019) Cheng (2019) Galf (2020) Gilmar (2018) Juanbetz (2017) Endo (2017) Eleireby (2021) Joashia (2022) Cheng (2021) Lincue (2018) Incue (2018) Incu	Doyle (2019)	23.10 (7.35, 38.85)	1.50
Cherg (2019) Cherg (2020) Graf (2020) Gilmar (2018) Andrade (2018) Juanbeltz (2017) Endo (2017) Shimzu (2018) Inomata (2022) Cher (2021) Eletraby (2021) Joshit (2021) Hino (2021) Eletraby (2021) Joshit (2021) Hino (2021) Eletraby (2021) Joshit (2021) Eletraby (2021) Eletraby (2021) Eletraby (2021) Joshit (2021) Eletraby (2021) Eletraby (2021) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Eletraby (2020) Zaw Graf (2020) Zaw Graf (2020) Subtotal (I-squared = 97.6%, p = 0.000) Just (2021) Chen (2021) Chen (2021) Subtotal (I-squared = 89.5%, p = 0.000) Typer Charl (2021) Chen (202	Jain (2019)	20.70 (8.23, 33.17)	1.67
Cheng (2019) Graf (2020) Gilmar (2018) Juanbetz (2017) Endo (2017) Endo (2017) Endo (2017) Endo (2017) Endo (2017) Endo (2017) Endo (2017) Endo (2021) Cheng (2021) Jobacha (2021) Jobacha (2021) Jobacha (2021) Lichtawa (2019) Innoue (2018) Innoue (2018) Inno	Cheng (2019)	18.10 (0.83, 35.37)	1.42
Graf (2020) 21.70 (6.79, 36.61) 1.55 Andrade (2018) 14.60 (1.04, 28.16) 122 Andrade (2017) 14.60 (1.04, 28.16) 122 Endo (2017) 18.91 (11.17, 26.65) 190 Shimizu (2018) 10.38 (4.00, 18.76) 198 Icoma (2022) 10.38 (4.00, 18.76) 198 Chen (2021) 30.01 (4.84, 21.16) 199 Joshita (2022) 13.00 (4.84, 21.16) 199 Chen (2021) 33.35 (22.88, 37.81) 202 Joshita (2020) 14.00 (10.59, 30.21) 199 Hono (2021) 20.88 (37.81) 202 Joshita (2021) 20.86 (12.23, 29.00) 188 Inoue (2018) 10.02 (4.41.76) 1.84 Inoue (2018) 10.02 (4.20.81) 10.58 (4.22, 28.16) 15.50 (12.88, 37.41) Diego (2023) 20.00 (14.44, 8.154) 14.50 14.60 Zdw 27.77 (1.75, 28.69) 19.75 19.75 Graf (2020) 15.00 (10.88, 25.02) 20.30 14.00 (12.87, 15.13) 20.80 Coloral (1-squared = 97.6%, p = 0.000) 15.00 (12.86, 11.16) 17.75 25.00 (13.14, 3.866) 17.	Cheng (2019)	16.20 (8.25, 24.15)	1.89
Gilmar (2018) 14.60 (1.04, 28.16) 1.62 Andrade (2018) 17.40 (7.67, 27.13) 181 Juanbetz (2017) 184 19.91 (1.17, 28.65) 19.90 Endo (2017) 19.81 19.91 (1.17, 28.65) 19.90 Shmizu (2018) 10.93 (4.00, 16.76) 19.96 Inomata (2022) 11.90 (4.84, 21.16) 19.99 Eletreby (2021) Joshta (2021) 19.93 (4.84, 21.16) 19.99 Jashta (2021) Joshta (2021) 19.93 (6.88, 9.7.81) 20.02 Jeltreby (2021) Joshta (2021) 11.91, 22.83 19.99 Jos (6.12, 30, 29.00) 18.8 28.20 (14.44, 8.41.92) 11.91 Inoue (2018) 11.00 (4.48, 4.1.6) 19.99 Inoue (2018) 11.90 (4.82, 4.1.6) 19.90 Inoue (2018) 11.50 (-4.25, 27.25) 15.00 Inoue (2023) 20.97 (11.55, 29.80) 14.55 Juanbetz (2021) 20.87 (11.59, 29.80) 14.55 Leixee (2020) 11.50 (-4.25, 27.25) 15.00 Dayle (2018) 11.50 (-4.25, 27.25) 15.00 Inoue (2018) 11.50 (-4.25, 27.25) 15.00 <	Graf (2020)	21.70 (6.79, 36.61)	1.55
Andrade (2018) Juanelate (2017) Endo (2017) Endo (2017) Shimizu (2018) Inomata (2022) Chen (2021) Dismita (2022) Chen (2021) Joshita (2022) Chen (2021) Joshita (2020) Abdoa (2020) Hino (2021) Hino (2021) Abdoa (2020) Hino (2021) Abdoa (2020) Abdoa (2020) Dego (2023) Subtotal (I-squared = 97.6%, p = 0.000) Averola (2018) Insue (2018) Insue (2018) Insue (2018) Insue (2018) Insue (2018) Insue (2018) Insue (2018) Gitto (2018) Beig (2018) Munoz L (2020) Nevola (2020) Averola (2020) Typear Gilmar (2018) Gitto (2018) Beig (2018) Munoz L (2020) Chen (2021) Lotikawa (2019) Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) Averall (I-squared = 97.0%, p = 0.000) MUNZE Weights are from random effects analysis	Gilmar (2018)	14.60 (1.04, 28.16)	1.62
Juanbetz (2017) Endo (2017) Endo (2017) Shimizu (2018) Inomata (2022) Chen (2021) Abdoa (2020) Hino (2021) Abdoa (2020) Hino (2021) Ichikawa (2019) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2021) Disstitutal (-squared = 97.6%, p = 0.000) Zdw Graf (2020) There is a straight of the	Andrade (2018)	17.40 (7.67, 27.13)	1.81
Endo (2017) Endo (2017) Shimizu (2018) Shimizu (2013) Chen (2021) Eletreby (2021) Joshita (2022) Chen (2021) Eletreby (2021) Joshita (2020) Hino (2021) Hino (2021) Ichikawa (2019) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Chego (2023) Ammed (2023) Dego (2023) Zaw Graf (2020) Zaw Graf (2020) Degis (2021) Jossa (2021) Ammed (2023) Dego (2023) Subtotal (I-squared = 89.5%, p = 0.000) Verall (I-squared = 97.0%, p = 0.001) NOTE: Weights are from random effects analysis	Juanbeltz (2017)	22.00 (16.29, 27.71)	1.98
Endo (2017) Shimizu (2018) Inomata (2022) Chen (2022) Chen (2021) Joshia (2021) Abdoa (2020) Hino (2021) Hino (2021) Hino (2021) Hino (2021) Inoue (2018) Class (2023) Subtotal (I-squared = 97.6%, p = 0.000) Zdw Graf (2020) Carl (2018) Carl (2020) Carl (2020)	Endo (2017)	18.91 (11.17, 26.65)	1.90
Shimizu (2018) 5.30 (-8.69, 19.20) 1.50 Inomata (2022) 1.200 (8.28, 17.32) 2.22 Chen (2021) 3.30 (-8.49, 17.32) 2.22 Abda (2020) 1.50 9.82 (93.78, 103.86) 2.00 Joshta (2021) 3.35 (-8.49, 7.31) 2.00 3.35 (-8.49, 7.31) 2.02 Abda (2020) 1.80 9.82 (93.78, 103.86) 2.00 3.35 (-8.49, 7.41) 2.00 Ihou (2018) 1.00ue (2018) 2.00 (1.68, 2.50.2) 2.03 1.61 Inoue (2023) 1.62 (-2.4, 2.81.6) 1.65 1.65 1.64 1.69 Degic (2023) 1.50 (1.58, 2.50.2) 2.03 1.50 (1.68, 2.50.2) 2.03 1.50 1.68 1.64 Doyle (2019) 15.50 (1.22, 1.84.5) 1.65 1.65 1.68 1.64 1.68 1.64 1.69 1.60 1.68 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 1.64 <td< td=""><td>Endo (2017)</td><td>10.38 (4.00. 16.76)</td><td>1.96</td></td<>	Endo (2017)	10.38 (4.00. 16.76)	1.96
Inomata (202) Dren (2021) Chen (2021) 13.00 (4.84, 21.16) Jashita (2021) 33.35 (28.89, 37.81) Abdoa (2020) 19.90 (4.84, 21.16) Hino (2021) 20.65 (12.30, 28.09, 37.81) Linklawa (2019) 20.65 (12.30, 28.00, 01.188) Inoue (2018) 16.00 (0.39, 02.10) Inoue (2018) 15.20 (2.42, 8.16) Dayle (2023) 20.87 (11.95, 29.80) Subtotal (I-squared = 97.6%, p = 0.000) 25.00 (13.14, 36.86) Z4w 25.70 (9.64, 41.76) 1.48 Griaf (2020) 25.70 (9.64, 41.76) 1.48 Dayle (2018) 11.50 (4.25, 27.25) 1.50 Inoue (2018) 11.50 (4.25, 27.25) 1.50 Inoue (2018) 25.00 (13.14, 36.86) 1.71 Inoue (2018) 11.50 (4.45, 27.25) 1.50 Inoue (2018) 11.50 (4.45, 27.25) 1.50 Inoue (2018) 11.50 (4.42, 21.76) 1.48 Inoue (2018) 11.50 (4.42, 27.75) 1.50 Inoue (2021) 25.00 (13.41, 36.86) 1.71 Inoue (2018) 11.50 (4.25, 27.25) 1.50 Inoue (2018) 11.50 (4.2	Shimizu (2018)	5 30 (-8 69 19 29)	1.59
 Lincher (2021) Liehteky (2021) Joshita (2020) Hino (2021) Abdoa (2020) Hino (2021) Abdoa (2020) Hino (2021) Loikawa (2019) Inoue (2018) Subtotal (I-squared = 97.6%, p = 0.000) Loikawa (2019) Subtotal (I-squared = 97.0%, p = 0.001) Loisas (2021) Nevola (2020) Subtotal (I-squared = 97.0%, p = 0.001) Loisas (2021) Nevola (2020) Subtotal (I-squared = 97.0%, p = 0.001) Loisas (2021) Nevola (1-squared = 97.0%, p = 0.001) Loisas (2021) Nevola (I-squared = 97.0%, p = 0.001) Norreall (I-squared = 97.0%, p = 0.001) NOTE: Weights are from random effects analysis 	Inomata (2022)	12 80 (8 28 17 32)	2 02
Chief (2221) 100 (19, 22, 10) 100 (19, 22, 10) Joshiti (2021) 33.35 (28, 99, 37, 81) 2.00 Jashiti (2021) 33.35 (28, 99, 37, 81) 2.00 Jinou (2021) 20.65 (12.30, 29.00) 18 Inoue (2018) 20.04 (10.59, 30.21) 181 Inoue (2018) 20.02 (24, 28.16) 1.65 Iosa (2021) 44.84, 49.22) 1.99 Jiego (2023) 5.00 (0.31, 12.29) 1.99 Anmed (2023) 15.35 (12.25, 18.45) 2.05 Subtatal (I-squared = 97.6%, p = 0.000) 5.20 (11.98, 25.02) 2.03 Caraf (2020) 25.70 (9.64, 41.76) 1.48 Doyle (2019) 11.50 (4.25, 27.25) 1.50 Ichikawa (2019) 10.00 (13.14, 36.86) 1.77 Inoue (2018) 30.0 (1.30, 42.61) 1.72 Gito (2021) 25.00 (12.86, 37.14) 1.77 Inoue (2018) 11.00 (19.87, 22.13) 2.06 Gito (2021) 20.00 (19.87, 12.10) 1.50 Inoue (2018) 13.00 (13.92, 42.61) 1.72 Gito (2021) 20.00 (19.87, 12.13) 2.08 Ichikawa (2019) 1.00	Chen (2021)	13.00 (4.84, 21.16)	1 80
Late by (221) Jabria (2021) Abdoa (2020) Hino (2021) Abdoa (2020) Hino (2021) Ichikawa (2019) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Ahmed (2023) Diego (2023) Subtotal (I-squared = 97.6%, p = 0.000) Year Gilmar (2018) Bossa (2021) Nevola (2020) Subtotal (I-squared = 89.5%, p = 0.000) Year Gilmar (2018) Beig (2021) Nevola (2020) Subtotal (I-squared = 89.5%, p = 0.000) Year Gilmar (2018) Beig (2018) Munoz, H (2020) Chenikawa (2019) Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) Year Gilmar (2018) Beig (2018) Munoz, H (2020) Chenikawa (2019) Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) Year Gilmar (2018) Beig (2018) Munoz, H (2020) Chenikawa (2019) Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) Tyear Gilmar (2018) Beig (2018) Munoz, H (2020) Chenikawa (2019) Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) Tyear Gilmar (2018) Beig (2018) Munoz, H (2020) Chenikawa (2019) Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) NOTE: Weidhts are from random effects analysis	Eletroby (2021)		2.00
Joshina (2021) 33.33 (26.68, 07.61) 2.12 Hino (2021) 11,122,133 199 Linkawa (2019) 20.65 (12.30, 29.00) 188 Inoue (2018) 20.014,48,41.92 1.61 Inoue (2018) 12.04,28,109 1.61 Inoue (2023) 15.20 (2.24, 28.16) 1.65 Jammed (2023) 15.20 (2.24, 28.16) 1.65 Jammed (2023) 20.87 (11.95, 29.80) 45.5 Z4w Graf (2020) 25.70 (9.64, 41.76) 1.48 Doyle (2019) 25.00 (13.14, 36.86) 1.71 Inoue (2018) 25.00 (13.43, 36.86) 1.71 Inoue (2018) 23.00 (14.46, 31.54) 1.87 Gitto (2021) 23.00 (14.46, 31.54) 1.87 Inoue (2018) 13.00 (1.39, 24.61) 1.72 Sangineto (2021) 23.00 (14.46, 31.54) 1.87 Inoue (2018) 13.00 (1.97, 22.13) 2.08 Issa (2021) 1.40 (19.87, 22.13) 2.08 Issa (2021) 23.00 (14.46, 31.54) 1.87 Beig (2018) 34.60 (24.34, 44.86) 1.79 Gilmar (2018) 26.90 (12.65, 41.15)		\sim 30.02 (30.70, 103.00) 22.25 (29.90, 27.91)	2.00
Audual (2020) 17.37 (11.91, 22.63) 1.93 Hino (2021) 28.20 (14.48, 41.92) 1.81 Inoue (2018) 28.20 (14.48, 41.92) 1.81 Inoue (2018) 7.60 (-0.26, 15.46) 1.90 Inoue (2018) 7.60 (-0.26, 15.46) 1.90 Inoue (2018) 7.60 (-0.26, 15.46) 1.90 Diego (2023) 21.00 (16.98, 25.02) 2.03 Subtotal (I-squared = 97.6%, p = 0.000) 20.87 (11.95, 29.80) 45.5 24w 25.70 (9.64, 41.76) 1.48 Doyle (2019) 11.50 (-4.25, 27.25) 1.50 Inoue (2018) 11.00 (16.98, 31.54) 1.77 Inoue (2018) 11.00 (1.90, 9.40) 1.88 Inoue (2018) 11.00 (1.98, 19.12) 2.03 Inoue (2018) 11.00 (1.98, 19.12) 2.03 Isoutotal (I-squared = 89.5%, p = 0.000) 17.98 (14.16, 21.80) 18.11 Gilmar (2018) 34.60 (24.34, 44.86) 1.79 Beig (2018) 34.60 (24.34, 44.86) 1.79 Murcal (2020) 14.30 (5.30, 23.30) 1.85 Chen (20		17 27 (11 01 22 22)	1.02
Fill(b)(2021) 20.053 (12.30, 29.00) 1.86 Inoue (2018) 10.002 (2018) 28.20 (14.48, 41.92) 1.61 Inoue (2018) 7.60 (0.26, 15.46) 1.90 Iossa (2021) Ahmed (2023) 15.20 (2.24, 28.16) 1.65 Subtotal (1-squared = 97.6%, p = 0.000) 5.20 (2.24, 28.16) 1.65 Z4w 5.20 (2023) 6.30 (0.31, 12.29) 1.97 Graf (2020) 20.87 (11.95, 29.80) 45.51 2.65 Doyle (2019) 25.70 (9.64, 41.76) 1.48 Inoue (2018) 20.00 (14.46, 31.54) 1.68 Doyle (2019) 25.70 (9.64, 41.76) 1.48 Inoue (2018) 25.00 (13.14, 2.90 (19.44, 25, 27.25) 1.50 Inoue (2018) 25.00 (13.14, 30.68) 1.71 Inoue (2018) 23.00 (14.46, 31.54) 1.87 Sangineto (2021) 20.80 (14.46, 31.54) 1.87 Vevola (2020) 14.00 (12.87, 15.13) 2.08 Subtotal (I-squared = 89.5%, p = 0.000) 17.98 (14.16, 21.80) 18.11 Ivear 6.30 (-15.6, 14.16) 1.99 1.50 Beig (2018) 26.90 (12.65, 41.15) 1.58		17.37 (11.91, 22.03)	1.99
Ichikawa (2019) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2021) Ahmed (2023) Diego (2023) Subtotal (I-squared = 97.6%, p = 0.000) 2dw Graf (2020) Dyle (2019) Ichikawa (2019) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Sagnineto (2021) Nevola (2020) Subtotal (I-squared = 89.5%, p = 0.000)		20.65 (12.30, 29.00)	1.88
Indue (2018) Indue (2018) Indue (2018) Indue (2018) Indue (2018) Indue (2023) Diego (2023) Subtotal (I-squared = 97.6%, p = 0.000) 24w Graf (2020) 24w Graf (2020) 24w Graf (2020) 24w Graf (2020) 11.50 (-4.25, 27.25) 1.50 11.50 (-4.25, 27.25) 1.50 11.50 (-4.25, 27.25) 1.50 11.50 (-4.25, 27.25) 1.50 11.10 (2.80, 19.40) 11.50 (-4.25, 27.25) 1.50 11.10 (2.80, 19.40) 11.20 (13.8, 24.61) 17.20 11.10 (2.80, 19.40) 188 10.00 (2018) 11.00 (13.9, 24.61) 17.20 (19.8, 15.41) 17.23 angineto (2021) 10.50sa (2021) Nevola (2020) Subtotal (I-squared = 89.5%, p = 0.000) 14.00 (12.87, 15.13) 2.08 Subtotal (I-squared = 89.5%, p = 0.000) 14.30 (5.30, 23.30) 15.00 (1.56, 41.15) 1.58 26.90 (12.65, 41.15) 1.58 20.90 (12.65, 41.15) 1.59 1.50 1.737 (10.15, 24.59) 10.7	Ichikawa (2019)	28.20 (14.48, 41.92)	1.61
Incue (2018) Incue (2018) Incue (2018) Incue (2018) Incue (2023) Subtotal (I-squared = 97.6%, p = 0.000)	Inoue (2018)	20.40 (10.59, 30.21)	1.81
Incue (2018) lossa (2021) Ahmed (2023) Diego (2023) Subtotal (I-squared = 97.6%, p = 0.000) 24w Graf (2020) Doyle (2019) lchikawa (2019) Incue (2018) Incue (2021) Subtotal (I-squared = 89.5%, p = 0.000) Year Gilmar (2018) Beig (2018) Beig (2018) Beig (2018) Subtotal (I-squared = 89.5%, p = 0.000) Year Gilmar (2018) Beig (2018) Subtotal (I-squared = 89.5%, p = 0.000) Year Oglimar (2018) Beig (2018) Beig (2018) Beig (2018) Beig (2018) Subtotal (I-squared = 89.5%, p = 0.000) Year Gilmar (2018) Beig (2018) Bei	Inoue (2018)	7.60 (-0.26, 15.46)	1.90
lossa (2021) Ahmed (2023) Diego (2023) Subtotal (I-squared = 97.6%, p = 0.000) 24w Graf (2020) Doyle (2019) Ichikawa (2019) Inoue (2018) Inoue (2018) Inoue (2018) Inoue (2018) Subtotal (I-squared = 89.5%, p = 0.000) Year Gilmar (2018) Beig (2018) Subtotal (I-squared = 89.5%, p = 0.000) Year Gilmar (2018) Beig (2018) Chen (2021) Chen (2021) Chen (2021) Coverall (I-squared = 97.0%, p = 0.001) Overall (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis	Inoue (2018)	15.20 (2.24, 28.16)	1.65
Ahmed (2023) Diego (2023) Subtotal (I-squared = 97.6%, p = 0.000) 24w Graf (2020) Lchikawa (2019) Inoue (2018) Inoue (2018) Subtotal (I-squared = 89.5%, p = 0.000) Munoz.H (2020) Subtotal (I-squared = 89.5%, p = 0.000) Chen (2021) Ichikawa (2019) Inoue (2018) Subtotal (I-squared = 97.0%, p = 0.000) Overall (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis	lossa (2021)	21.00 (16.98, 25.02)	2.03
Diego (2023) Subtotal (I-squared = 97.6%, p = 0.000) 24w Graf (2020) Doyle (2019) Ichikawa (2019) Inoue (2018) Inoue (2018) Inoue (2018) Sangineto (2021) Subtotal (I-squared = 89.5%, p = 0.000) Year Gilmar (2018) Beig (2018) Subtotal (I-squared = 97.0%, p = 0.001) Overall (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis Diego (2023) Subtotal (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis	Ahmed (2023)	6.30 (0.31, 12.29)	1.97
Subtotal (I-squared = 97.6%, p = 0.000)	Diego (2023)	15.35 (12.25, 18.45)	2.05
24w Graf (2020) Doyle (2019) Ichikawa (2019) Inoue (2018) Inoue (2018) Inoue (2018) Sangineto (2021) Ogitto (2019) Subtotal (I-squared = 89.5%, p = 0.000) Year Gilmar (2018) Beig (2018) Beig (2018) Chen (2021) Ichikawa (2019) Ichikawa (2019) Doyle (2020) Subtotal (I-squared = 89.5%, p = 0.000) Year Gilmar (2018) Beig (2018) Dego (2023) Subtotal (I-squared = 77.0%, p = 0.001) Overall (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis	Subtotal (I-squared = 97.6%, p = 0.000)	20.87 (11.95, 29.80)	45.53
24W 25.70 (9.64, 41.76) 1.48 Doyle (2019) 11.50 (-4.25, 27.25) 1.50 Ichikawa (2019) 25.00 (13.14, 36.86) 1.71 Inoue (2018) 26.50 (15.86, 37.14) 1.77 Inoue (2018) 11.00 (2.80, 19.40) 1.88 Inoue (2018) 23.00 (14.46, 31.54) 1.87 Sangineto (2021) 21.00 (19.87, 22.13) 2.08 Iossa (2021) 15.00 (10.88, 19.12) 2.03 Nevola (2020) 15.00 (10.88, 19.12) 2.03 Inoue (2018) 26.90 (12.65, 41.15) 1.58 Beig (2018) 34.60 (24.34, 44.86) 1.79 Munoz.H (2020) 14.30 (5.30, 23.30) 1.85 Cheikawa (2019) 12.00 (-2.21, 26.21) 1.58 Diego (2023) 14.35 (11.25, 17.45) 2.05 Subtotal (I-squared = 97.0%, p = 0.001) 17.37 (10.15, 24.59) 10.71 . . . 19.08 (15.42, 22.73) 100.1 NOTE:	24w		
Doyle (2019) 11.50 (4.25, 27.25) 1.50 Ichikawa (2019) 11.50 (4.25, 27.25) 1.50 Ichikawa (2019) 25.00 (13.14, 36.86) 1.71 Inoue (2018) 11.60 (4.26, 27.25) 1.50 Inoue (2018) 11.60 (4.26, 27.25) 1.50 Sangineto (2021) 26.00 (13.14, 36.86) 1.71 Inoue (2018) 11.60 (4.26, 27.25) 1.50 Sangineto (2021) 23.00 (14.46, 31.54) 1.72 Iossa (2021) 21.00 (19.87, 22.13) 2.08 Iossa (2021) 15.00 (10.88, 19.12) 2.03 Nevola (2020) 14.00 (12.87, 15.13) 2.08 Subtotal (I-squared = 89.5%, p = 0.000) 17.98 (14.16, 21.80) 18.11 .1year 26.90 (12.65, 41.15) 1.58 Beig (2018) 26.90 (12.65, 41.15) 1.58 Munoz.H (2020) 14.30 (5.30, 23.30) 1.85 Chei (2021) 12.00 (-2.21, 26.21) 1.58 Ichikawa (2019) 12.00 (-2.21, 26.21) 1.58 Diego (2023) 14.35 (11.25, 17.45) 2.05 Subtotal (I-squared = 97.0%, p = 0.000) 19.08 (15.42, 22.73) 100.1	Graf (2020)	25 70 (9 64 41 76)	1 48
Correctory 11.30 (4.20, 27.20) 1.30 Ichikawa (2019) 25.00 (13.14, 36.86) 1.71 Inoue (2018) 11.00 (4.20, 27.20) 1.80 Inoue (2018) 11.00 (1.99, 24.61) 1.72 Gitto (2018) 13.00 (13.9, 24.61) 1.72 Gitto (2018) 23.00 (14.46, 31.54) 1.87 Sangineto (2021) 23.00 (14.46, 31.54) 1.87 Iossa (2021) 15.00 (10.88, 19.12) 2.03 Nevola (2020) 14.00 (12.87, 15.13) 2.08 Subtotal (I-squared = 89.5%, p = 0.000) 17.98 (14.16, 21.80) 18.11 </td <td>Dovle (2019)</td> <td>11 50 (-1 25 27 25)</td> <td>1 50</td>	Dovle (2019)	11 50 (-1 25 27 25)	1 50
Dimona (2013) 25.00 (13.14, 30.60) 1.71 Inoue (2018) 26.50 (15.86, 37.14) 1.77 Inoue (2018) 13.00 (1.39, 24.61) 1.72 Sangineto (2021) 23.00 (14.46, 31.54) 1.87 Iossa (2021) 21.00 (19.87, 22.13) 2.08 Nevola (2020) 15.00 (10.88, 19.12) 2.03 Subtotal (I-squared = 89.5%, p = 0.000) 17.98 (14.16, 21.80) 18.11 17.98 (14.16, 21.80) 18.11 Year Gilmar (2018) 26.90 (12.65, 41.15) 1.58 Beig (2018) 26.90 (12.65, 41.15) 1.58 Beig (2018) 26.90 (12.65, 41.15) 1.58 Diego (2023) 14.30 (5.30, 23.30) 1.85 Cheixava (2019) 12.00 (-2.21, 26.21) 1.58 Diego (2023) 14.35 (11.25, 17.45) 2.05 Subtotal (I-squared = 97.0%, p = 0.001) 19.08 (15.42, 22.73) 100.1 NOTE: Weights are from random effects analysis 19.08 (15.42, 22.73) 100.1		25 00 (12 1/ 26 06)	1.50
100ue (2019) 20.30 (15.00, 37.14) 1.77 Inoue (2018) 11.10 (280, 19.40) 1.88 Inoue (2018) 13.00 (1.39, 24.61) 1.72 Gitto (2013) 23.00 (14.46, 31.54) 1.72 Sangineto (2021) 21.00 (19.87, 22.13) 2.08 Iossa (2021) 15.00 (10.88, 19.12) 2.03 Nevola (2020) 14.00 (12.87, 15.13) 2.08 Subtotal (I-squared = 89.5%, p = 0.000) 17.98 (14.16, 21.80) 18.11 Iyear . . . Gilmar (2018) 26.90 (12.65, 41.15) 1.58 Beig (2018) 34.60 (24.34, 44.86) 1.79 Munoz.H (2020) 14.30 (5.30, 23.30) 1.85 Cheikawa (2019) 12.00 (-2.21, 26.21) 1.58 Diego (2023) 14.35 (11.25, 17.45) 2.05 Subtotal (I-squared = 97.0%, p = 0.001) 		20.00 (10.14, 00.00) DE EN (15 DE 07 44)	1.71
Indue (2016) 11.10 (2.80, 19.40) 1.88 Indue (2018) 13.00 (13.9, 24.61) 1.72 Gitto (2018) 23.00 (14.46, 31.54) 1.87 Sangineto (2021) 23.00 (14.46, 31.54) 1.87 Iossa (2021) 15.00 (10.88, 19.12) 2.03 Nevola (2020) 14.00 (12.87, 15.13) 2.08 Subtotal (I-squared = 89.5%, p = 0.000) 17.98 (14.16, 21.80) 18.11 </td <td></td> <td>∠0.00 (10.00, 07.14)</td> <td>1.77</td>		∠0.00 (10.00, 07.14)	1.77
Indue (2016) Gitto (2018) Sangineto (2021) Sangineto (2021) Nevola (2020) Subtotal (I-squared = 89.5%, p = 0.000) 1year Gilmar (2018) Beig (2018) Beig (2018) Munoz.H (2020) Chen (2021) Lohikawa (2019) Diego (2023) Subtotal (I-squared = 77.0%, p = 0.001) Overall (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis		11.10 (2.80, 19.40)	1.88
Gillo (2010) 23.00 (14.46, 31.54) 1.87 Sangineto (2021) lossa (2021) 21.00 (19.87, 22.13) 2.08 Nevola (2020) 15.00 (10.88, 19.12) 2.03 Subtotal (I-squared = 89.5%, p = 0.000) 17.98 (14.16, 21.80) 18.11 1year 26.90 (12.65, 41.15) 1.58 Beig (2018) 26.90 (12.65, 41.15) 1.58 Munoz.H (2020) 44.30 (5.30, 23.30) 1.85 Chen (2021) 6.30 (-1.56, 14.16) 1.90 Ichikawa (2019) 12.00 (-2.21, 26.21) 1.58 Diego (2023) 14.35 (11.25, 17.45) 2.05 Subtotal (I-squared = 97.0%, p = 0.001) 17.37 (10.15, 24.59) 10.77 . . 19.08 (15.42, 22.73) 100.1 NOTE: Weights are from random effects analysis 19.08 (15.42, 22.73) 100.1		13.00 (1.39, 24.01)	1.72
Sangineto (2021) lossa (2021) Nevola (2020) Subtotal (I-squared = 89.5%, p = 0.000)		23.00 (14.46, 31.54)	1.8/
iossa (2021) 15.00 (10.88, 19.12) 2.03 Nevola (2020) 14.00 (12.87, 15.13) 2.08 Subtotal (I-squared = 89.5%, p = 0.000) 17.98 (14.16, 21.80) 18.11 1year 26.90 (12.65, 41.15) 1.58 Beig (2018) 34.60 (24.34, 44.86) 1.79 Munoz, H (2020) 14.30 (5.30, 23.30) 1.85 Chen (2021) 6.30 (-1.56, 14.16) 1.90 Ichikawa (2019) 12.00 (-2.21, 26.21) 1.58 Diego (2023) 14.35 (11.25, 17.45) 2.05 Subtotal (I-squared = 77.0%, p = 0.001) 19.08 (15.42, 22.73) 100.1 NOTE: Weights are from random effects analysis	Sangineto (2021)	21.00 (19.87, 22.13)	2.08
Nevola (2020) Subtotal (I-squared = 89.5%, p = 0.000) 1. 1year Gilmar (2018) Beig (2018) Munoz.H (2020) Chen (2021) Ichikawa (2019) Diego (2023) Subtotal (I-squared = 77.0%, p = 0.001) Overall (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis	lossa (2021)	15.00 (10.88, 19.12)	2.03
Subtotal (I-squared = 89.5%, p = 0.000)	Nevola (2020)	14.00 (12.87, 15.13)	2.08
Jyear Gilmar (2018) Beig (2018) Munoz.H (2020) Chen (2021) Ichikawa (2019) Diego (2023) Ucoverall (I-squared = 77.0%, p = 0.001) Overall (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis	Subtotal (I-squared = 89.5%, p = 0.000)	17.98 (14.16, 21.80)	18.10
() cont 26.90 (12.65, 41.15) 1.58 Beig (2018) 34.60 (24.34, 44.86) 1.79 Munoz, H (2020) 14.30 (5.30, 23.30) 1.85 Chen (2021) 6.30 (-1.56, 14.16) 1.90 Lichikawa (2019) 12.00 (-2.21, 26.21) 1.58 Diego (2023) 14.35 (11.25, 17.45) 2.05 Subtotal (I-squared = 77.0%, p = 0.001) 17.37 (10.15, 24.59) 10.7 19.08 (15.42, 22.73) 100.1 NOTE: Weights are from random effects analysis 	1vear		
Contract (2016) 20.90 (12.05, 41.15) 1.58 Beig (2018) 34.60 (24.34, 44.86) 1.79 Munoz.H (2020) 14.30 (5.30, 23.30) 1.85 Chen (2021) 6.30 (-1.56, 14.16) 1.90 Ichikawa (2019) 12.00 (-2.21, 26.21) 1.58 Diego (2023) 14.35 (11.25, 17.45) 2.05 Subtotal (I-squared = 77.0%, p = 0.001) 17.37 (10.15, 24.59) 10.71 . . 19.08 (15.42, 22.73) 100.1 NOTE: Weights are from random effects analysis . . .	Gilmar (2019)	26 00 (12 65 41 45)	1 50
Detg (2010) 34.60 (24.34, 44.86) 1.79 Munoz.H (2020) 14.30 (5.30, 23.30) 1.85 Chen (2021) 6.30 (-1.56, 14.16) 1.90 Ichikawa (2019) 12.00 (-2.21, 26.21) 1.58 Diego (2023) 14.35 (11.25, 17.45) 2.05 Overall (I-squared = 97.0%, p = 0.001) 17.37 (10.15, 24.59) 10.71 Overall (I-squared = 97.0%, p = 0.000) 19.08 (15.42, 22.73) 100.1		20.90 (12.00, 41.15)	1.58
Invitrio: 14.30 (5.30, 23.30) 1.85 Chen (2021) 6.30 (-1.56, 14.16) 1.90 Ichikawa (2019) 12.00 (-2.21, 26.21) 1.58 Diego (2023) 14.35 (11.25, 17.45) 2.05 Subtotal (I-squared = 77.0%, p = 0.001) 17.37 (10.15, 24.59) 10.7 Overall (I-squared = 97.0%, p = 0.000) 19.08 (15.42, 22.73) 100.1		34.60 (24.34, 44.86)	1.79
Chen (2021) Ichikawa (2019) Diego (2023) Subtotal (I-squared = 77.0%, p = 0.001) Overall (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis	Munoz.H (2020)	14.30 (5.30, 23.30)	1.85
Ichikawa (2019) 12.00 (-2.21, 26.21) 1.58 Diego (2023) 14.35 (11.25, 17.45) 2.05 Subtotal (I-squared = 77.0%, p = 0.001) 17.37 (10.15, 24.59) 10.79 Overall (I-squared = 97.0%, p = 0.000) 19.08 (15.42, 22.73) 100.100	Chen (2021)	6.30 (-1.56, 14.16)	1.90
Diego (2023) 14.35 (11.25, 17.45) 2.05 17.37 (10.15, 24.59) 10.7: Overall (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis	Ichikawa (2019)	12.00 (-2.21, 26.21)	1.58
Subtotal (I-squared = //.0%, p = 0.001) Overall (I-squared = 97.0%, p = 0.000) NOTE: Weights are from random effects analysis		14.35 (11.25, 17.45)	2.05
Overall (I-squared = 97.0%, p = 0.000) 19.08 (15.42, 22.73) 100.0 NOTE: Weights are from random effects analysis 10.0 10.0	Subtotal (I-squared = 77.0%, p = 0.001)	17.37 (10.15, 24.59)	10.75
NOTE: Weights are from random effects analysis	Overall (I-squared = 97.0%, p = 0.000)	19.08 (15.42, 22.73)	100.0
	NOTE: Weights are from random effects analysis	,	
104 0 404	101 0	104	

Fig. 3 Forest plot of serum LDL changes after treatment at each time point

ID	WMD (95% CI)	% Wei
ETO El Sagheer (2018) Graf (2020) Gilmar (2018) Juanbeltz (2017) Pedersen (2016) Pedersen (2016) Munoz. H (2020) Eletreby (2021) Iossa (2021) Nevola (2020) Anca (2023) Subtotal (I-squared = 70.1%, p = 0.000)	3.50 (1.75, 5.25) -0.40 (-5.33, 4.53) 0.20 (-6.69, 7.09) 0.00 (-2.86, 2.86) 2.00 (-5.03, 9.03) 7.90 (0.00, 15.80) -4.40 (-10.35, 1.55) -0.28 (-3.01, 2.45) -4.00 (-6.30, -1.70) 0.00 (-0.59, 0.59) -0.85 (-3.99, 2.29) -0.03 (-1.60, 1.54)	2.78 1.85 1.36 2.48 1.33 1.16 2.52 2.64 2.96 2.40 23.0
4w Chida (2018) Endo (2017) Endo (2017) Subtotal (I-squared = 0.0%, p = 0.989)	7.00 (1.58, 12.42) 6.61 (1.98, 11.24) 6.49 (2.05, 10.93) 6.66 (3.91, 9.42)	1.72 1.94 2.00 5.65
12w Chida (2018) Doyle (2019) Jain (2019) Cheng (2019) Graf (2020) Gilmar (2018) Juanbeltz (2017) Endo (2017) Shimizu (2018) Inomata (2022) Chen (2021) Joshita (2021) Joshita (2021) Joshita (2021) Inoue (2018) Inoue (2013) Diego (2023) Subtotal (I-squared = 87.2%, p = 0.000)	8.00 (2.23, 13.77) 3.90 (-5.31, 13.11) 2.80 (-1.43, 7.03) 5.10 (-4.31, 14.51) 0.30 (-4.33, 4.93) 2.70 (-2.69, 8.09) 2.61 (-4.79, 10.01) 2.00 (-0.86, 4.86) 4.96 (0.50, 9.42) 4.99 (0.50, 9.48) 9.90 (3.31, 16.49) 4.50 (2.36, 6.64) 0.60 (-4.23, 5.43) -2.23 (-4.90, 0.44) 8.35 (5.97, 10.73) 2.38 (0.68, 4.08) 2.18 (-5.21, 9.57) 4.30 (-1.06, 9.66) 1.00 (-3.83, 5.83) 3.50 (-3.42, 10.42) -3.00 (-5.45, -0.55) 12.82 (10.63, 15.01) -0.84 (-2.44, 0.76) 3.40 (1.36, 5.44)	$\begin{array}{c} 1.63\\ 0.95\\ 2.060\\ 0.92\\ 1.94\\ 1.72\\ 1.22\\ 2.48\\ 1.99\\ 1.68\\ 1.88\\ 2.55\\ 2.66\\ 2.79\\ 1.26\\ 1.68\\ 1.33\\ 2.66\\ 2.66\\ 2.66\\ 2.81\\ 1.34\\ 1.34\\ 2.66\\ 2.81\\ 1.34\\ 1.88\\ 1.34\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88\\ 1.88$
24w Graf (2020) Doyle (2019) Ichikawa (2019) Inoue (2018) Inoue (2018) Inoue (2018) Gitto (2018) Iossa (2021) Nevola (2020) Subtotal (I-squared = 81.5%, p = 0.000)	4.00 (-1.43, 9.43) 7.70 (-1.51, 16.91) 3.18 (-4.68, 11.04) 7.30 (0.91, 13.69) 0.40 (-4.62, 5.42) 11.40 (4.44, 18.36) 2.00 (-2.92, 6.92) 2.00 (-0.34, 4.34) -2.00 (-2.59, -1.41) 3.16 (0.18, 6.14)	1.71 0.95 1.17 1.47 1.83 1.34 1.86 2.63 2.96 15.9
1year Gilmar (2018) Beig (2018) Munoz.H (2020) Chen (2021) Ichikawa (2019) Diego (2023) Subtotal (I-squared = 56.4%, p = 0.043)	3.01 (4.16, 10.18) 3.90 (-2.51, 10.31) -4.60 (-10.54, 1.34) -4.70 (-9.16, -0.24) 5.40 (-2.98, 13.78) 1.10 (-0.48, 2.68) 0.14 (-2.93, 3.20)	1.30 1.47 1.58 1.99 1.08 2.81 10.2
Overall (I-squared = 86.6%, p = 0.000)	2.40 (1.31, 3.48)	100

Fig. 4 Forest plot of serum HDL changes after treatment at each time point

ID		WMD (95% CI)	% Weight
ETO El Sagheer (2018) Graf (2020) Gilmar (2018) Pedersen (2016) Pedersen (2016) Munoz.H (2020) Eletreby (2021) Iossa (2021) Nevola (2020) Anca (2023) Subtotal (I-squared = 98.8%, p = 0.000)	٠	-18.80 (-29.41, -8.19) -8.40 (-33.95, 17.15) -12.10 (-31.93, 7.73) -1.90 (-25.54, 21.74) -9.80 (-31.93, 12.33) -4.00 (-16.77, 8.77) 81.05 (75.19, 86.91) 5.00 (0.91, 9.09) -1.00 (-2.59, 0.59) -2.22 (-12.26, 7.82) 3.40 (-15.91, 22.72)	2.52 2.04 2.25 2.11 2.16 2.47 2.61 2.63 2.65 2.54 23.98
	•	$\begin{array}{c} 44.20 \ (4.10, 84.30) \\ 1.50 \ (-21.64, 24.64) \\ 5.50 \ (-21.34, 32.34) \\ 9.90 \ (-2.19, 21.99) \\ -9.10 \ (-35.44, 17.24) \\ 1.50 \ (-20.07, 23.07) \\ -3.00 \ (-17.36, 11.36) \\ 10.10 \ (-13.75, 33.95) \\ -24.40 \ (42.06, -6.74) \\ 5.50 \ (-7.71, 18.71) \\ 15.80 \ (3.88, 27.72) \\ 113.86 \ (107.45, 120.27) \\ -5.96 \ (-18.64, 6.72) \\ 3.60 \ (-20.16, 27.36) \\ -14.00 \ (-31.68, 3.68) \\ -4.30 \ (-17.15, 8.55) \\ 0.70 \ (-3.172, 33.12) \\ 5.00 \ (0.15, 9.85) \\ 9.70 \ (-1.01, 20.41) \\ -13.04 \ (-20.87, -5.21) \\ 7.62 \ (-12.89, 28.12) \end{array}$	1.52 2.13 1.99 2.01 2.18 2.42 2.40 2.42 2.46 2.49 7) 2.60 2.47 2.10 2.32 2.47 1.79 2.62 2.52 2.58 45.58
24w Graf (2020) Doyle (2019) Ichikawa (2019) Inoue (2018) Inoue (2018) Gitto (2018) Iossa (2021) Nevola (2020) Subtotal (I-squared = 0.0%, p = 0.488)		-11.40 (-37.82, 15.02) 44.20 (4.10, 84.30) 8.50 (-15.50, 32.50) -6.20 (-24.76, 12.36) -1.30 (-13.86, 11.26) -7.50 (-37.60, 22.60) 5.00 (-20.14, 30.14) 1.00 (-2.014, 30.14) -1.00 (-2.50, 0.50) -0.77 (-2.17, 0.63)	2.01 1.52 2.10 2.29 2.47 1.87 2.05 2.63 2.65 19.59
1year Gilmar (2018) Beig (2018) Munoz.H (2020) Chen (2021) Ichikawa (2019) Subtotal (I-squared = 0.0%, p = 0.861)		9.20 (-12.57, 30.97) 17.70 (-9.96, 45.36) 7.40 (-6.86, 21.66) 17.10 (4.01, 30.19) 7.10 (-24.24, 38.44) 12.24 (4.13, 20.36)	2.18 1.96 2.43 2.46 1.83 10.85
Overall (I-squared = 97.8%, p = 0.000) NOTE: Weights are from random effects		6.11 (-1.47, 13.69)	100.00

 $\textbf{Fig. 5} \hspace{0.1 cm} \textit{Forest plot of serum TG changes after treatment at each time point}$

Currently, the mechanism of the interaction and influence between HCV and blood lipids remains unclear. Previous studies have shown that inhibition of cholesteryl ester and triglyceride synthesis can inhibit viral infection by inhibiting the assembly process of hepatitis C virus [46].On the other hand, hepatitis C virus itself is a high-fat lipovirus particle, very similar to very lowdensity lipoprotein(VLDL), which can alter liver lipoprotein-related functions in a variety of ways, including by impairing the VLDL release pathway. Therefore, it is related to the accumulation of liver lipids and the pathogenesis of dyslipidemia [47]. Additionally, it can enhance replication by regulating host cell lipid metabolism [48]. In HCV patients who have achieved SVR, HCV RNA cannot be detected in the plasma, which may reduce lipid metabolism in the host and affect the patient's lipid levels. Currently, there are many treatments for HCV infection, but compared with traditional peginterferon-based treatment regimens, recent DAAs have increased the persistent viral response rate in HCV patients [49]. Furthermore, studies also have found that DAA treatment in HCV patients can lead to good cardiovascular outcomes while reducing the potential for insulin resistance and diabetes development [50-52].

There have been many studies on HCV treatment and lipid changes, but the results have not been the same. Stefan et al. [53] found that suppression and elimination of HCV by DAAs without interferon had no effect on TG but increased TC levels; however, interferon-based therapy increased TG and TC during treatment and led to elevated TC when a sustained virological response was achieved. DAAs therapy for hepatitis C is closely related to lipid changes in patients [31].

In 2021, RosannaVillani et al. [54]. conducted a metaanalysis in which they examined changes in blood lipid levels during DAA treatment and at 12 and 24 weeks after the end of treatment. The results showed that the patient's TC, LDL, and HDL levels increased, which persisted for 24 weeks after the end of treatment. The differences between this study and that of RosannaVillani et al. are as follows:1. Study population: the study population of Rosanna Villani et al. included patients treated with DAA, while this study targeted patients who achieved SVR after DAA treatment, which can exclude the effect of SVR on patients' blood lipids; 2. Observation time: R et al. analyzed the changes in blood lipids of patients from the treatment period to 24 weeks after treatment; this study was extended to 1 year after the end of treatment to observe further the long-term effects of DAA on patients' blood lipids. 3. Subgroup analysis: Further subgroup analysis was performed for different sustained viral response times and different genotypes in this study. 4. The inclusion of more studies in this meta-analysis made the results more robust.

Finally, the meta-analysis included 32 articles showing a correlation between persistent hepatitis C virus response and lipid changes. Analytical data showed that serum TC and LDL levels in HCV patients were significantly elevated from the end of treatment to one year after the end of treatment. At the same time, within 4 to 24 weeks after the end of DAA treatment, the patient's serum HDL level also increased significantly, but the TG level did not change significantly. In addition, AST and ALT levels also improved after treatment.

It can be seen that after hepatitis C patients achieve SVR by DAA treatment, the main changes in blood lipids are persistent increases in TC, LDL and HDL, while TG has no significant change. This may provide a reference for the treatment of lipid-lowering in HCV patients and the long-term detection of lipids.

Hepatitis C has a variety of genotypes, in this study, by analyzing the changes of lipids in patients with different genotypes who obtained SVR, it can be found that the levels of serum TC and LDL in patients with G1b, G1, G2 and G3 genotypes were all increased after treatment. Similarly, Jain et al. [55] demonstrated a significant increase in TC and LDL with SVR in HCV genotype 3 patients. And Doyle et al. [56] also found a significant increase in TC and LDL levels after achieving SVR in a study of genotype 1 patients. Antiviral therapy affects lipid metabolism [57], and the differences in the effects of different genotypes on blood lipids in patients with SVR seem to be inconclusive at present, which may require further research in the future.

In addition, a sensitivity analysis was conducted by excluding single studies. The sensitivity analysis did not affect the combined effect size by excluding single studies, suggesting that the results of the meta-analysis were robust.

Strengths and limitations

This study comprehensively analyzed the lipid changes in patients who achieved SVR after DAA treatment. The changes of lipid in patients with different genotypes and different SVR were also compared.

In addition, this study had some limitations. First, only English databases were selected for literature retrieval; Therefore, the scope of the selected literature was not wide enough, and the number of included studies was small. Further high-quality studies with larger samples size are required. Second, in some studies of this study showed significant heterogeneity. Although sensitivity analysis was conducted and a random effects model was finally adopted for analysis, the stability of the metaanalysis results may be affected to a certain extent. Third, there was a publication bias in part of the analysis process, which was identified and processed. Fourth, the age of the research population included in the literature is

Conclusion

In summary, this meta-analysis suggests that the sustained viral response induced by DAAs treatment in HCV patients is significantly associated with increased serum TC, LDL, and HDL levels and improvements in AST and ALT levels after treatment.

There were similar changes in serum TC and LDL levels in patients with and without cirrhosis. which provided a reference value for long-term lipid-lowering therapy in patients. Future research may focus on these changes and the choice of lipid-lowering therapies to reduce the incidence of fatty liver and cardiovascular disease.

Declarations.

Abbreviations

Applev	lations
DAAs	Direct-acting Antiviral drugs
HCV	Hepatitis C virus
SVR	Sustained Viral Response
TC	Total cholesterol
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
TG	Triglyceride
IFN	interferon
NOS	Newcastle Ottawa Scale
NA	Not available
AF	Advanced fibrosis
NAF	Non-advanced fibrosis
С	Cirrhotics
NC	Non-cirrhotics
SOF	Sofosbuvir
DCV	Daclatasvir
ASV	Asunaprevir
LDV	Ledipasvir
LDV	Ledipasvir
RBV	Ribavirin
SIM	Simeprevir
GZR	Grazoprevir
EBV	Elbasvir
PrOD	Paritaprevir/ritonavir/ombitasvir/dasabuvir
DAC	Daclatasvir

Supplementary Information

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Supplementary Material 1	
Supplementary Material 2	
Supplementary Material 3	
Supplementary Material 4	
Supplementary Material 5	

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Authors' contributions

Tingting Mei and Xiaojie Huang contributed equally to this study. Tingting Mei and Xiaojie Huang analyzed the data and wrote the manuscript. Menglu Liu and Shan Tang were involved in the data extraction process. Wenyan Zhang

participated in the literature screening. Haibin Yu conceptualized the topic and supervised and facilitated the conduct of the study. All authors reviewed the manuscript.

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Data Availability

The datasets used and/or analysed during the current study are available from the.

corresponding author on reasonable request.

Declarations

Consent for publication

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

This study did not require ethical approval because the meta analysis was based on published research and the original data wre anonymous.

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