



# Sofosbuvir and Ribavirin with or Without Pegylated-Interferon in Hepatitis C Virus Genotype-2 or -3 Infections: A Systematic Review and Meta-Analysis

Mohammad Ehsan Bayatpoor<sup>1,2,3,4</sup>, Mohammad Hossein Khosravi<sup>1,2,3,4</sup>, Heidar Sharafi<sup>1,3,4</sup>, Mohammad Saeid Rezaee-Zavareh<sup>1,2,3,4</sup>, Bita Behnava<sup>1,3,4</sup> and Seyed Moayed Alavian<sup>1,3,4,\*</sup>

<sup>1</sup>Baqiyatallah Research Center for Gastroenterology and Liver Diseases (BRCGL), Baqiyatallah University of Medical Sciences, Tehran, Iran

<sup>2</sup>Student Research Committee, Baqiyatallah University of Medical Sciences, Tehran, Iran

<sup>3</sup>Meta-Analysis Study Group, Iran Hepatitis Network, Tehran, Iran

<sup>4</sup>Middle East Liver Disease (MELD) Center, Tehran, Iran

\*Corresponding author: Baqiyatallah Research Center for Gastroenterology and Liver Diseases (BRCGL), Baqiyatallah University of Medical Sciences, Tehran, Iran. Tel: +98-2188945186, Fax: +98-2188945188, Email: alavian@thc.ir

Received 2018 May 21; Revised 2019 January 04; Accepted 2019 January 20.

## Abstract

**Background:** Direct-acting antiviral agents (DAAs) have changed the treatment landscape of hepatitis C virus (HCV) infection. Sofosbuvir (SOF), as a DAA inhibiting HCV NS5B polymerase, has found a remarkable contribution to the treatment regimens of HCV genotype-2 (HCV-2) and -3 infections.

**Objectives:** In this meta-analysis, we aimed to evaluate the efficacy of the combination of SOF and Ribavirin (RBV) with or without pegylated-interferon (PegIFN) in the treatment of HCV-2 and -3 infections.

**Methods:** In this meta-analysis, we searched electronic databases including PubMed, Scopus, ScienceDirect, and Web of Science using appropriate and relevant keywords. Based on the results of the heterogeneity test (chi-squared and I-squared), fixed- or random-effects models were used to calculate the pooled sustained virological response (SVR) rates.

**Results:** After removing duplicates and screening of 1408 articles, 16 studies were included in the quantitative synthesis. The pooled SVR rates calculated for the treatment of patients suffering HCV-2 infection were 91.2% (95% CI: 86.6% - 95.8%) using the SOF + RBV regimen for 12 weeks and 92.6% (95% CI: 87.1% - 98.1%) using the SOF + RBV + PegIFN regimen for 12 weeks. The pooled SVR calculated for the treatment of patients suffering HCV-3 infection was 53.1% (95% CI: 41% - 65.1%) using the SOF + RBV regimen for 12 weeks, 81.6% (95% CI: 74.4% - 88.7%) using the SOF + RBV regimen for 24 weeks, and 93.8% (95% CI: 86.9% - 100%) using the SOF + RBV + PegIFN regimen for 12 weeks.

**Conclusions:** The combination of SOF and BV with or without PegIFN for 12 weeks is highly efficacious (> 90%) for the treatment of patients with HCV-2 infection. However, for the treatment of patients with HCV-3 infection only would 12 weeks of SOF + PegIFN + RBV result in > 90% treatment success.

**Keywords:** Hepatitis C, Sofosbuvir, Ribavirin, Pegylated-Interferon, Meta-Analysis

## 1. Background

Involving approximately 2.8% of the general population worldwide, hepatitis C virus (HCV) infection is one of the most important public health concerns, which is estimated to affect 185 million people (1). A remarkable number of complications such as liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) have been recounted for chronic HCV infection (2). The majority of cases with HCV infection remain undiagnosed because of the asymptomatic nature of the disease (3). Nevertheless, nearly all of hepatitis C complications are preventable by treatment if

the disease is diagnosed at early phases (4). Approximately, 30% of patients with chronic hepatitis C (CHC) infection have HCV genotype-2 (HCV-2) or -3 (5).

Newly proposed medications for HCV infection have increased the possibility of successful therapy and have provided a wide range of choices for treatment. Various oral and injection medications have been approved for different HCV genotypes. The main goal of these treatments is to achieve a sustained virological response (SVR), which has made regimens with direct-acting antiviral agents (DAAs) superior to traditional pegylated-interferon (PegIFN) and ribavirin (RBV) combination therapy (6). The rate of SVR

to PegIFN and RBV combination therapy in patients with HCV-2 or -3 infections has been reported as 60% - 90% (7-11). The combination of Sofosbuvir (SOF) and RBV with or without PegIFN is being prescribed for the treatment of patients with HCV-2 or -3 and can lead to 60% to > 90% SVR (12-14). However, there is not a concise conclusion on the preference of each regimen. Therefore, the need for a review of the abundant relevant studies comes up to finally determine which regimen should be prescribed for each HCV genotype.

## 2. Objectives

In this systematic review and meta-analysis, we aimed to evaluate the efficacy of regimens of SOF plus RBV with or without PegIFN for the treatment of patients with HCV-2 or -3 infections.

## 3. Methods

### 3.1. Data Resources and Search Strategies

We systematically searched electronic databases including PubMed, Scopus, ScienceDirect, and Web of Science. We appropriately combined keywords of “Sofosbuvir”, “Sovaldi”, “GS-7977”, “Pegylated-interferon”, and “Ribavirin” for use in different databases (Appendix 1 in Supplementary File). Initially, our search was performed in September 2015 and we updated it in September 2016. The search language was restricted to English. In addition, for identifying any additional studies, we screened the reference lists of the ultimately included studies in this survey.

### 3.2. Eligibility Criteria

We included any cohort or clinical trial that evaluated the effect of 12- or 24-week therapy with SOF + RBV or SOF + RBV + PegIFN on the SVR rate of patients with HCV-2 or -3 infections. Patients co-infected with HBV or HIV and those with a history of kidney or liver transplantation, a history of treatment with DAAs, and decompensated cirrhosis (Child-Pugh B and C) were not considered for inclusion. All studies reporting SVR with the inclusion of more than 10 patients were included in the quantitative analysis; otherwise, they were excluded for the final quantitative analysis.

### 3.3. Study Selection, Quality Assessment, and Data Extraction

Two authors (M.E.B and M.H.K) independently investigated all identified papers through database searching and screening in different levels including title, abstract, and full-text. The screening process was completely based

on the PRISMA guideline for reporting of systematic reviews (15). Any disagreements between the authors were resolved by neutral discussion. Cochrane’s tool for risk of bias assessment (16) and Newcastle Ottawa scale (17) were applied for the evaluation of clinical trial and cohort studies, respectively. Data regarding publication details and study patients in each paper were extracted, including first author name, publication year, sample size, patients’ age, gender, baseline HCV RNA level, history of previous treatment, cirrhosis, and rate of SVR.

### 3.4. Data Analysis

We used STATA 11 for all statistical analyses in this survey. Based on the result of the test for heterogeneity (chi-squared and I-squared), fixed- or random-effects models were used with command “metaprop” for the calculation of the pooled SVR rate and 95% confidence interval (CI). In addition, Begg’s and Egger’s tests were used for the publication bias assessment. The publication bias analysis was not conducted because less than 10 studies were included.

## 4. Results

### 4.1. Study Screening

We found 1408 records through database searching and after removing duplicates, 1044 papers were investigated. We excluded 793 articles by title screening and 212 by abstract screening. Finally, together with the updated search, 16 papers were included in this study (Figure 1).

### 4.2. Risk of Bias Assessment

The results of quality assessment for the included clinical trial and cohort studies are shown in Tables 1 and 2, respectively. All clinical trials and cohort studies were categorized as low risk and high quality, respectively. No study was excluded based on this assessment.

**Table 2.** Quality Assessment of Cohort Studies Based on the New Castle Ottawa Scale

First Author (Reference)	Selection	Comparability	Exposure
Maasoumy, B. (24)	****	*	***
Steinebrunner, N. (25)	****	*	***
Jayasekera, C. R. (26)	***	*	***
Welzel, T. M. (27)	****	*	***
Cho, Y. (28)	***	*	***
Backus, L. I. (29)	****	*	***
Tacke, F. (30)	***	*	***

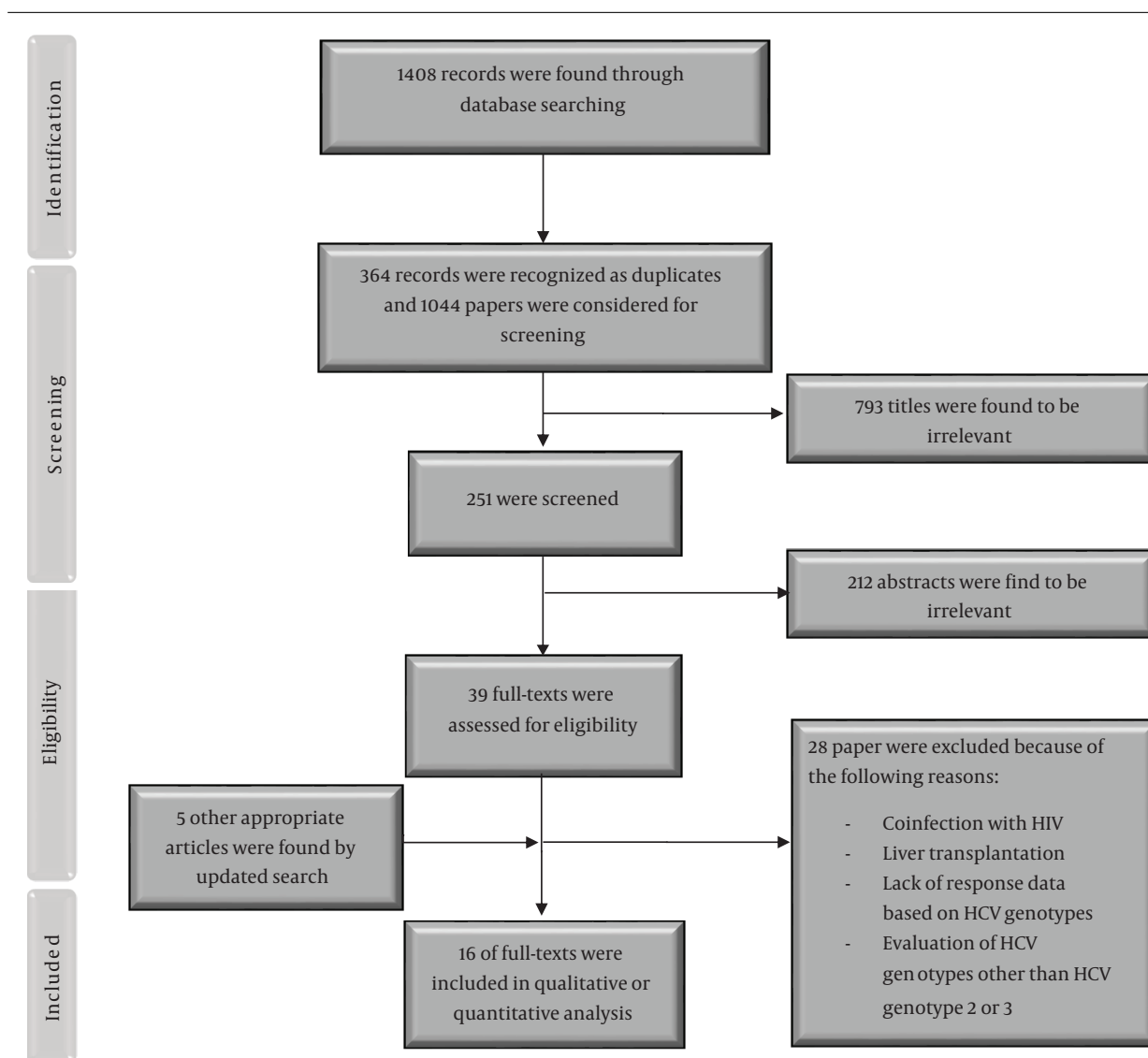


Figure 1. Screening of articles based on the PRISMA statement

#### 4.3. Characteristics of the Included Studies

The included studies were clinical trials and cohort studies published since 2012. The characteristics of the studies on the treatment of patients with HCV genotype-2 or -3 are shown in Tables 3 and 4, respectively.

#### 4.4. Outcome Evaluation

We evaluated two regimens for the treatment of patients with HCV-2 infection including SOF + RBV for 12 weeks and SOF + RBV + PegIFN for 12 weeks and three regimens for HCV-3 infection including SOF + RBV for 12 weeks, SOF + RBV for 24 weeks, and SOF + RBV + PegIFN for 12 weeks.

A summary of the results of the meta-analysis of these regimens is shown in Table 5.

##### 4.4.1. Treatment of HCV Genotype-2 with Sofosbuvir Plus Ribavirin for 12 Weeks

We found 12 studies (total sample size = 1776) evaluating the effect of 12-week treatment with SOF + RBV on patients with HCV-2 infection. Because of the existence of heterogeneity between the results of the included studies ( $\chi^2 = 116.82$ ,  $P = 0.00$ ,  $I^2 = 90.58\%$ ), we used a random-effects model that calculated the pooled SVR rate (95% CI) as 92% (87% - 96%) (Figure 2). The publication bias was assessed based on Begg's ( $P = 0.89$ ) and Egger's ( $P = 0.05$ ) tests and

**Table 3.** Characteristics of the Included Studies on the Treatment of Patients with HCV Genotype-2 Infection (Appropriate Arms and Groups in Each Study of the Treatment of HCV-Infected Patients with Sofosbuvir Plus Ribavirin with or Without Pegylated-Interferon)

First Author (Reference)	Treatment History	Publication Year	Sample Size	Mean Age (SD or Range)	Male Gender (%)	Treatment Regimen, Duration (Week)	Mean HCV RNA Level (SD or Range)	Cirrhosis (%)
Steinebrunner, N. (25)	Mix	2015	14	50 ± 12	ND	SOF + RBV, 12	3.23 ± 6.61	42
Omata, M. (14)	Mix	2014	153	57	54	SOF + RBV, 12	6.3 ± 0.84	11
Gane, J. E. (21)	ND	2013	4	47	ND	SOF + RBV, 12	6.7 (5.7 - 7.1)	ND
Lawitz, E. (20)	TN	2013	70	48 (20 - 72)	67	SOF + RBV, 12	6.0 ± 0.8	ND
Jacobson, I. M. (12)	TN	2013	109	52 (21 - 75)	ND	SOF + RBV, 12	6.3 ± 0.77	ND
Zeuzem, S. (19)	Mix	2014	73	58 (28 - 74)	55	SOF + RBV, 12	6.5 ± 0.7	15
Welzel, T. M. (27)	Mix	2016	283	59 (21 - 80)	61.5	SOF + RBV, 12	6.3	21.9
Ahn, S. H. (23)	Mix	2016	129	55	45	SOF + RBV, 12	6 ± 1	10
Kao, J-H. (13)	Mix	2016	87	53	41	SOF + RBV, 12	6.4 ± 0.91	15
Cho, Y. (28)	ND	2015	6	52	50	SOF + RBV, 12	6.2	50
Backus, L. I. (29)	Mix	2015	619	60.9 ± 7.0	96	SOF + RBV, 12	6.2 ± 0.8	ND
Massoumy, B. (24)	Mix	2016	32	53.5	53	SOF + RBV, 12	6.08 (1.18 - 7.78)	31.2
Jayasekera, C. R. (26)	Mix	2015	16	62.8	43	SOF + RBV, 12	ND	31.2
Tacke, F. (30)	Mix	2016	191	53 (19 - 85)	62	SOF + RBV, 12	ND	19
Foster, G. R. (18)	TE	2015	16	50 ± 10.2	68	SOF + RBV + PegIFN, 12	6.3 ± 0.69	100
Lawitz, E. (22)	TE	2015	23	58	61	SOF + RBV + PegIFN, 12	6.4 ± 0.7	61
Gane, J. E. (21)	ND	2013	4	46 (37 - 57)	82	SOF + RBV + PegIFN, 12	6.5 (5.1 - 7.3)	0

Abbreviations: ND, not determined; PegIFN, pegylated-interferon; RBV, ribavirin; SD, standard deviation; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment naïve.

showed a considerable bias.

#### 4.4.2. Treatment of HCV Genotype-2 with Sofosbuvir Plus Ribavirin and Pegylated-Interferon for 12 Weeks

We included two studies in the meta-analysis of 12-week treatment with SOF + RBV + PegIFN in patients with HCV-2 (total sample size = 39). Since the heterogeneity was not seen between the results of these two studies ( $\chi^2 = 0.0$ ,  $P = 0.95$ ,  $I^2 = 0.0\%$ ), we applied a fixed-effects model that calculated the pooled SVR rate (95% CI) as 95% (85% - 100%) (Figure 3).

#### 4.4.3. Treatment of HCV Genotype-3 with Sofosbuvir Plus Ribavirin for 12 Weeks

Three studies (total sample size = 292) were evaluated for the regimen of SOF + RBV in patients with HCV-3. Our results showed heterogeneity ( $\chi^2 = 4.55$ ,  $P = 0.10$ ,  $I^2 = 56\%$ )

and based on random-effects model, the pooled SVR rate (95% CI) was calculated as 55% (44% - 66%) (Figure 4).

#### 4.4.4. Treatment of HCV Genotype-3 with Sofosbuvir Plus Ribavirin for 24 Weeks

Three studies were included in the meta-analysis of the SOF + RBV regimen for 24 weeks in patients with HCV-3 (total sample size = 465). Heterogeneity was found in the results of the included studies ( $\chi^2 = 7.74$ ,  $P = 0.02$ ,  $I^2 = 74.16\%$ ); therefore, the random-effects model was used. The SVR rate (95% CI) was calculated as 81% (72% - 88%) (Figure 5).

#### 4.4.5. Treatment of HCV Genotype-3 with Sofosbuvir Plus Ribavirin and Pegylated-Interferon for 12 Weeks

We included three studies (total sample size = 221) assessing the effect of 12-week treatment with SOF + RBV + PegIFN on patients with HCV-3. Heterogeneity was not

**Table 4.** Characteristics of the Included Studies on the Treatment of Patients with HCV Genotype-3 Infection (Appropriate Arms and Groups in Each Study of the Treatment of HCV-Infected Patients with Sofosbuvir Plus Ribavirin with or Without Pegylated-Interferon)

First Author (Reference)	Treatment History	Publication Year	Sample Size	Mean Age (SD or Range)	Male Gender (%)	Treatment regimen, Duration (week)	Mean HCV RNA Level (SD or Range)	Cirrhosis (%)
Zeuzem, S. (19)	Mix	2013	11	46	55	SOF + RBV, 12	6.2 ± 0.8	18
Jacobson, I. M. (12)	ND	2012	98	52	57	SOF + RBV, 12	6.3 ± 0.77	21
Lawitz, E. (20)	ND	2012	183	48 (20 - 72)	67	SOF + RBV, 12	6.0 ± 0.8	ND
Jayasekera, C. R. (26)	Mix	2015	6	62	50	SOF + RBV, 24	ND	33.3
Maasoumy, B. (24)	Mix	2016	33	50	67	SOF + RBV, 24	6.08	47.6
Foster, G. R. (18)	Mix	2015	182	49 ± 9.8	65	SOF + RBV, 24	6.2 ± 0.71	37
Zeuzem, S. (19)	Mix	2013	250	48 (19 - 69)	62	SOF + RBV, 24	6.3 ± 0.7	24
Massoumy, B. (24)	Mix	2016	16	49.5	62.5	SOF + RBV + PegIFN, 12	5.94	37.5
Foster, G. R. (18)	Mix	2015	181	50 ± 10.2	67	SOF + RBV + PegIFN, 12	6.3 ± 0.69	38
Lawitz, E. (22)	TE	2013	24	54 (39 - 64)	75	SOF + RBV + PegIFN, 12	6.0 ± 0.6	50
Gane, J. E. (21)	ND	2013	7	46 (37 - 57)	82	SOF + RBV + PegIFN, 12	6.5 (5.1 - 7.3)	0

Abbreviations: SD, standard deviation; ND, not determined; TE, treatment-experienced; TN, treatment naïve; SOF, sofosbuvir; RBV, ribavirin; PegIFN, pegylated-interferon

**Table 5.** A Summary of the Results of Meta-Analysis of the Evaluated Treatment Regimens

HCV Genotype	Treatment Regimen	Treatment Duration, Week	Number of Included Studies, n	Sample Size, n	SVR, %	Lower CI of SVR, %	Upper CI of SVR, %
HCV-2	SOF + RBV	12	12	1776	92	87	96
HCV-2	SOF + RBV + PegIFN	12	2	39	95	85	100
HCV-3	SOF + RBV	12	3	292	55	44	66
HCV-3	SOF + RBV	24	3	465	81	72	88
HCV-3	SOF + RBV + PegIFN	12	3	221	93	85	99

Abbreviations: ND, not determined; PegIFN, pegylated-interferon; RBV, ribavirin; SD, standard deviation; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment naïve.

found between their results ( $\chi^2 = 0.08$ ,  $P = 0.13$ ,  $I^2 = 50.97\%$ ); therefore, we used fixed-effects model that pooled calculated the SVR rate (95% CI) as 93% (85% - 99%) (Figure 6).

## 5. Discussion

In this meta-analysis, we found that SOF + RBV ± PegIFN regimen could be effective in most patients with HCV-2 or 3 infections. Although the previous standard of care with PegIFN and RBV combination therapy was more effective in patients with HCV-2 or -3 infections than in those with HCV-1 or -4 infections (8, 9, 11) and resulted even up to a

90% SVR, the long-term antiviral therapy, the side-effects of PegIFN and RBV, and the contraindication of PegIFN and RBV in conditions such as cirrhosis made the treatment of patients infeasible with low treatment uptake and patient adherence (31). In recent years, the development of DAAs for the treatment of HCV infection has changed the standard of care for the treatment of patients with HCV infection (32-34). The introduction of SOF as a pangenotypic inhibitor of HCV NS5B polymerase was the first step in the improvement of HCV-2 or 3 treatment (32). The addition of SOF to RBV with or without PegIFN resulted in the increased response rate to therapy in patients with HCV-2 or

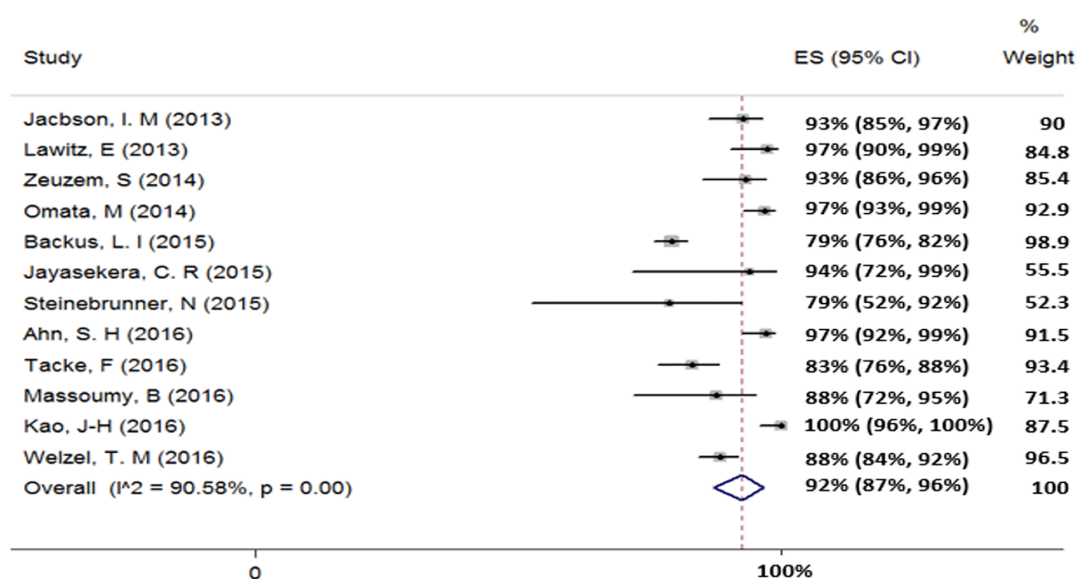


Figure 2. The pooled rate of SVR for 12-week treatment with sofosbuvir plus ribavirin in patients with HCV genotype-2

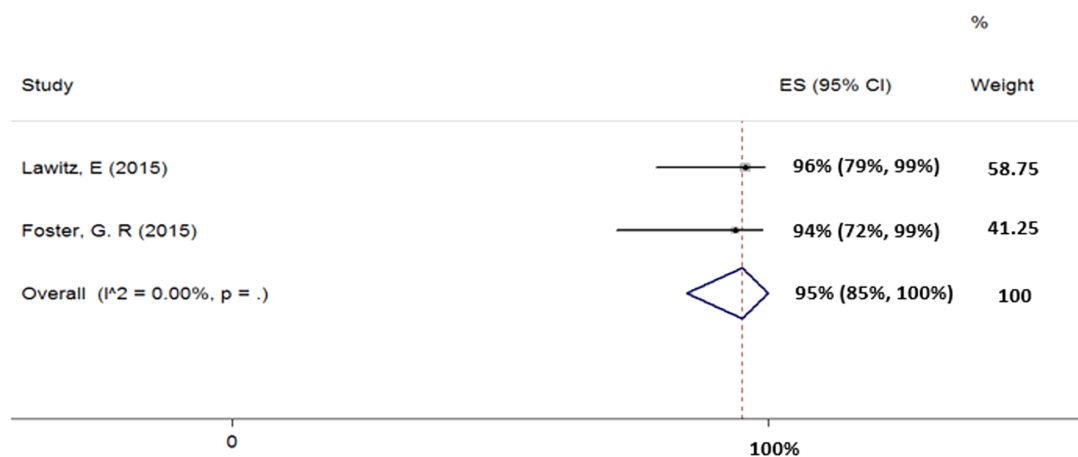


Figure 3. The pooled rate of SVR for 12-week treatment with sofosbuvir plus ribavirin and pegylated-interferon in patients with HCV genotype-2

-3, with a shorter duration of treatment and fewer treatment complications compared to PegIFN + RBV (19).

In this study, we pooled the data of study/study arms for two regimens of SOF + RBV and SOF + RBV + PegIFN, both for 12 weeks, in patients with HCV-2 infection. Interestingly, the response rate was not significantly different between the two above-mentioned regimens (91.23% vs. 92.59%), making the IFN-free SOF + RBV for 12 weeks superior for the treatment of patients with HCV-2 infection. Regarding the

treatment of HCV-3 infection, three regimens of SOF + RBV + PegIFN for 12 weeks and SOF + RBV for 12 and 24 weeks were assessed. The treatment of HCV-3 patients with SOF + RBV for 12 weeks resulted in a suboptimal response rate of 53.08% while the prolongation of the combination therapy with SOF + RBV to 24 weeks increased the response rate to 81.56%. Furthermore, SOF + RBV + PegIFN for 12 weeks resulted in a 93.82% response rate in patients with HCV-3 and thus, this regimen was superior in terms of higher re-

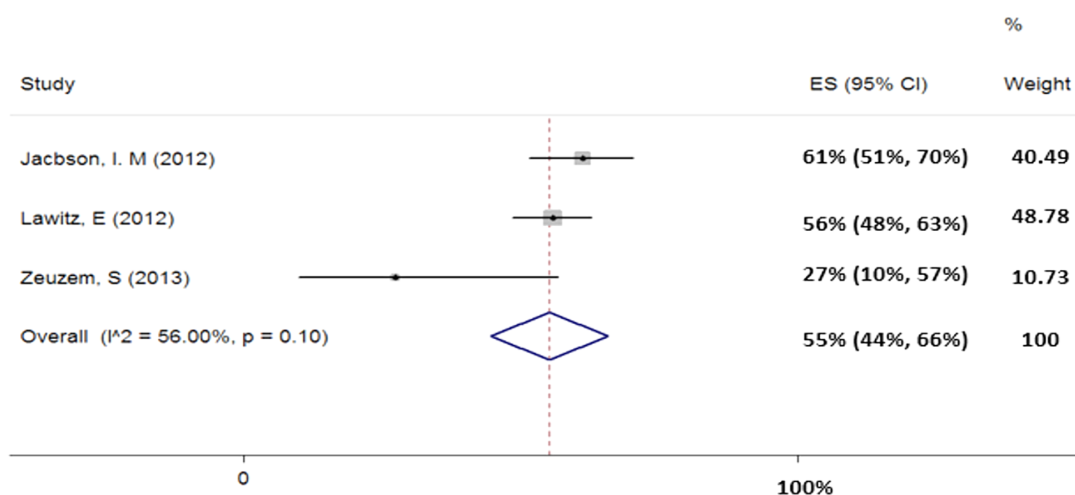


Figure 4. The pooled rate of SVR for 12-week treatment with sofosbuvir plus ribavirin in patients with HCV genotype-3

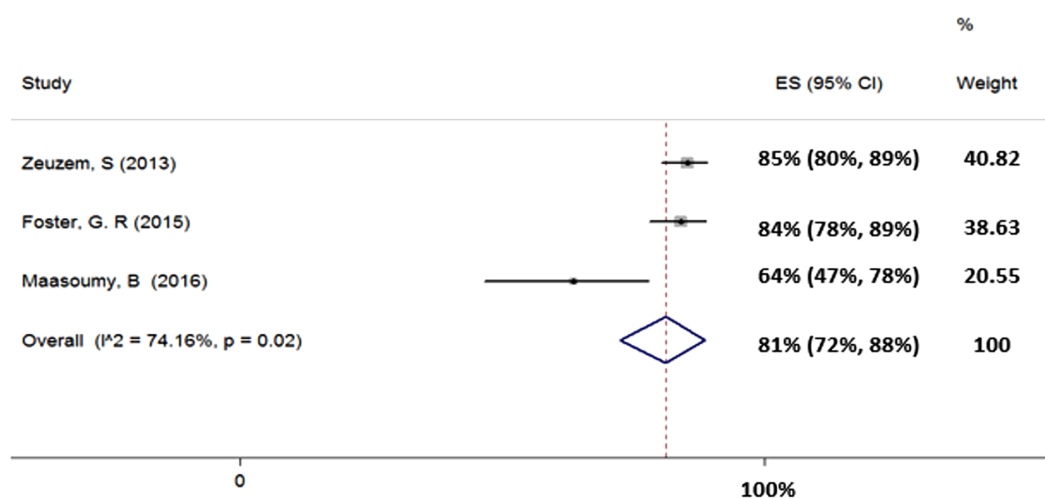


Figure 5. The pooled rate of SVR for 24-week treatment with sofosbuvir plus ribavirin in patients with HCV genotype-3

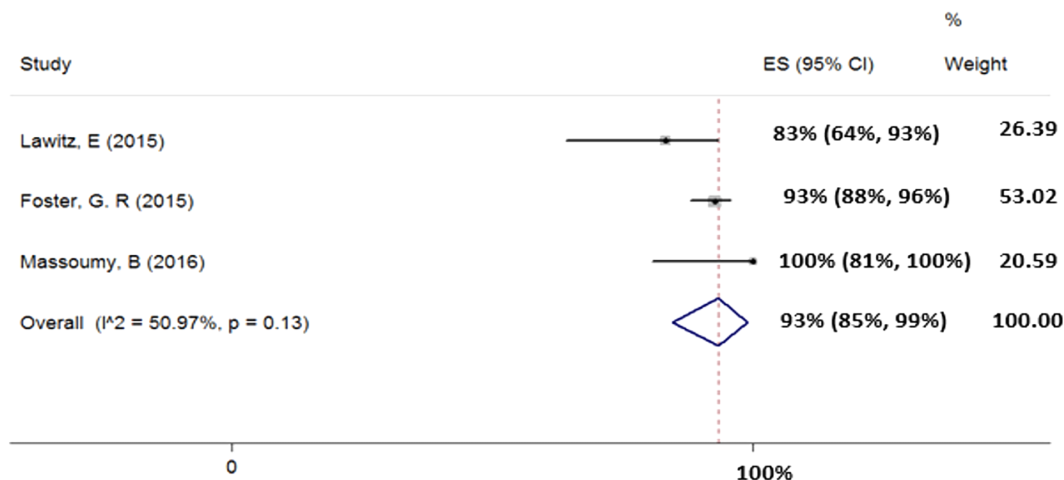
sponses compared to the two other regimens of SOF + RBV in patients with HCV-3 infection.

The introduction and approval of daclatasvir (DCV), an NS5A inhibitor of HCV, were other steps in the optimization of the treatment of HCV-2 or -3 infection with an increase in the SVR rate to more than 95% (35). The regimen of SOF + DCV can be administered in non-cirrhotic and treatment-naïve patients with HCV-3 infection for 12 weeks while patients with a history of treatment or advanced liver disease should be treated with the addition of RBV and/or the prolongation of the treatment course. More recently, the combination of SOF/velpatasvir (VEL) was approved for

the treatment of HCV infection as a pangenotypic regimen (32). Although these two IFN-free regimens are more efficient than the regimen of SOF + RBV ± PegIFN in patients with HCV-2 or -3, DCV and SOF/VEL are not available and affordable in most developing countries and resource-limited settings where the frequency of HCV infection is high. Fortunately, SOF, RBV, and PegIFN are manufactured in many countries as generic drugs at reasonable prices.

In conclusion, the combination of SOF and RBV with or without PegIFN for 12 weeks is highly efficacious (> 90%) for the treatment of patients with HCV-2 infection. However, for the treatment of patients with HCV-3 infection,





**Figure 6.** The pooled rate of SVR for 12-week treatment with sofosbuvir plus ribavirin and pegylated-interferon in patients with HCV genotype-3

only would 12 weeks of SOF + RBV + PegIFN result in > 90% treatment success. With all of these new regimens of anti-HCV treatment, there is great hope for the global elimination of hepatitis C by 2030.

### Supplementary Material

Supplementary material(s) is available [here](#) [To read supplementary materials, please refer to the journal website and open PDF/HTML].

### Footnotes

**Conflict of Interests:** We declare no conflict of interest.

**Funding/Support:** We declare no financial support.

### References

- Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. *Hepatology*. 2013;**57**(4):1333-42. doi: [10.1002/hep.26141](#). [PubMed: [23172780](#)].
- Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med*. 2001;**345**(1):41-52. doi: [10.1056/NEJM200107053450107](#). [PubMed: [11439948](#)].
- Edlin BR, Winkelstein ER. Can hepatitis C be eradicated in the United States? *Antiviral Res*. 2014;**110**:79-93. doi: [10.1016/j.antiviral.2014.07.015](#). [PubMed: [25110202](#)].
- Kamal-Yanni M. Hepatitis C drug affordability. *Lancet Glob Health*. 2015;**3**(2):e73-4. doi: [10.1016/S2214-109X\(14\)70365-1](#). [PubMed: [25617196](#)].
- Tapper EB, Afdhal NH. Is 3 the new 1: Perspectives on virology, natural history and treatment for hepatitis C genotype 3. *J Viral Hepat*. 2013;**20**(10):669-77. doi: [10.1111/jvh.12168](#). [PubMed: [24010641](#)].
- Adinolfi LE, Guerrera B. All-oral interferon-free treatments: The end of hepatitis C virus story, the dream and the reality. *World J Hepatol*. 2015;**7**(22):2363-8. doi: [10.4254/wjh.v7.i22.2363](#). [PubMed: [26464751](#)]. [PubMed Central: [PMC4598606](#)].
- Haj-Sheykholeslami A, Keshvari M, Sharafi H, Pouryasyn A, Hemmati K, Mohammadzadehparjikelaei F. Interferon-lambda polymorphisms and response to pegylated interferon in Iranian hepatitis C patients. *World J Gastroenterol*. 2015;**21**(29):8935-42. doi: [10.3748/wjg.v21.i29.8935](#). [PubMed: [26269684](#)]. [PubMed Central: [PMC4528037](#)].
- Keshvari M, Alavian SM, Behnava B, Pouryasyn A, Craig JC, Sharafi H. Impact of IFNL4 rs12979860 and rs8099917 polymorphisms on response to peg-interferon-alpha and ribavirin in patients with congenital bleeding disorder and chronic hepatitis C. *J Clin Lab Anal*. 2017;**31**(4). doi: [10.1002/jcla.22063](#). [PubMed: [27735085](#)].
- Behnava B, Sharafi H, Keshvari M, Pouryasyn A, Mehrnough L, Salimi S, et al. The role of polymorphisms near the IL28B gene on response to peg-interferon and ribavirin in thalassemic patients with hepatitis C. *Hepat Mon*. 2016;**16**(1). e32703. doi: [10.5812/hepatmon.32703](#). [PubMed: [27110259](#)]. [PubMed Central: [PMC4834189](#)].
- Heidrich B, Wiegand SB, Buggisch P, Hinrichsen H, Link R, Moller B, et al. Treatment of naive patients with chronic hepatitis C genotypes 2 and 3 with pegylated interferon alpha and ribavirin in a real world setting: Relevance for the new era of DAA. *PLoS One*. 2014;**9**(10). e108751. doi: [10.1371/journal.pone.0108751](#). [PubMed: [25302676](#)]. [PubMed Central: [PMC4193764](#)].
- Keshvari M, Alavian SM, Behnava B, Pouryasyn A, Sharafi H. The interferon lambda 4 rs368234815 predicts treatment response to pegylated-interferon alpha and ribavirin in hemophilic patients with chronic hepatitis C. *J Res Med Sci*. 2016;**21**:72. doi: [10.4103/1735-1995.189678](#). [PubMed: [27904617](#)]. [PubMed Central: [PMC512234](#)].
- Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;**368**(20):1867-77. doi: [10.1056/NEJMoa1214854](#). [PubMed: [23607593](#)].
- Kao JH, Chien RN, Chang TT, Peng CY, Hu TH, Lo GH, et al. A phase 3b study of sofosbuvir plus ribavirin in Taiwanese patients with chronic genotype 2 hepatitis C virus infection. *Liver Int*. 2016;**36**(8):1101-7. doi: [10.1111/liv.13082](#). [PubMed: [26835876](#)]. [PubMed Central: [PMC5071670](#)].



14. Omata M, Nishiguchi S, Ueno Y, Mochizuki H, Izumi N, Ikeda F, et al. Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: An open-label, phase 3 trial. *J Viral Hepat.* 2014;**21**(11):762-8. doi: [10.1111/jvh.12312](https://doi.org/10.1111/jvh.12312). [PubMed: [25196837](https://pubmed.ncbi.nlm.nih.gov/25196837/)].
15. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann Intern Med.* 2009;**151**(4):264-9. W64. [PubMed: [19622511](https://pubmed.ncbi.nlm.nih.gov/19622511/)].
16. Higgins JPT. *Cochrane handbook for systematic reviews of interventions version 5.0.2*. The Cochrane Collaboration; 2008.
17. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Ottawa Hospital Research Institute; 2019.
18. Foster GR, Pianko S, Brown A, Forton D, Nahass RG, George J, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. *Gastroenterology.* 2015;**149**(6):1462-70. doi: [10.1053/j.gastro.2015.07.043](https://doi.org/10.1053/j.gastro.2015.07.043). [PubMed: [26248087](https://pubmed.ncbi.nlm.nih.gov/26248087/)].
19. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med.* 2014;**370**(21):1993-2001. doi: [10.1056/NEJMoa1316145](https://doi.org/10.1056/NEJMoa1316145). [PubMed: [24795201](https://pubmed.ncbi.nlm.nih.gov/24795201/)].
20. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med.* 2013;**368**(20):1878-87. doi: [10.1056/NEJMoa1214853](https://doi.org/10.1056/NEJMoa1214853). [PubMed: [23607594](https://pubmed.ncbi.nlm.nih.gov/23607594/)].
21. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med.* 2013;**368**(1):34-44. doi: [10.1056/NEJMoa1208953](https://doi.org/10.1056/NEJMoa1208953). [PubMed: [23281974](https://pubmed.ncbi.nlm.nih.gov/23281974/)].
22. Lawitz E, Poordad F, Brainard DM, Hyland RH, An D, Dvory-Sobol H, et al. Sofosbuvir with peginterferon-ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. *Hepatology.* 2015;**61**(3):769-75. doi: [10.1002/hep.27567](https://doi.org/10.1002/hep.27567). [PubMed: [25322962](https://pubmed.ncbi.nlm.nih.gov/25322962/)]. [PubMed Central: [PMC4365682](https://pubmed.ncbi.nlm.nih.gov/PMC4365682/)].
23. Ahn SH, Lim YS, Lee KS, Paik SW, Lee YJ, Jeong SH, et al. A phase 3b study of sofosbuvir plus ribavirin in treatment-naive and treatment-experienced Korean patients chronically infected with genotype 2 hepatitis C virus. *J Viral Hepat.* 2016;**23**(5):358-65. doi: [10.1111/jvh.12499](https://doi.org/10.1111/jvh.12499). [PubMed: [26864153](https://pubmed.ncbi.nlm.nih.gov/26864153/)].
24. Maasoumy B, Vermehren J, Welker MW, Bremer B, Perner D, Honer Zu Siederdisen C, et al. Clinical value of on-treatment HCV RNA levels during different sofosbuvir-based antiviral regimens. *J Hepatol.* 2016;**65**(3):473-82. doi: [10.1016/j.jhep.2016.04.006](https://doi.org/10.1016/j.jhep.2016.04.006). [PubMed: [27085252](https://pubmed.ncbi.nlm.nih.gov/27085252/)].
25. Steinebrunner N, Sprinzl MF, Zimmermann T, Worns MA, Zimmerer T, Galle PR, et al. Early virological response may predict treatment response in sofosbuvir-based combination therapy of chronic hepatitis c in a multi-center "real-life" cohort. *BMC Gastroenterol.* 2015;**15**:97. doi: [10.1186/s12876-015-0328-9](https://doi.org/10.1186/s12876-015-0328-9). [PubMed: [26239732](https://pubmed.ncbi.nlm.nih.gov/26239732/)]. [PubMed Central: [PMC4523924](https://pubmed.ncbi.nlm.nih.gov/PMC4523924/)].
26. Jayasekera CR, Perumpail RB, Chao DT, Pham EA, Aggarwal A, Wong RJ, et al. Task-shifting: An approach to decentralized hepatitis C treatment in medically underserved areas. *Dig Dis Sci.* 2015;**60**(12):3552-7. doi: [10.1007/s10620-015-3911-6](https://doi.org/10.1007/s10620-015-3911-6). [PubMed: [26467703](https://pubmed.ncbi.nlm.nih.gov/26467703/)].
27. Welzel TM, Nelson DR, Morelli G, Di Bisceglie A, Reddy RK, Kuo A, et al. Effectiveness and safety of sofosbuvir plus ribavirin for the treatment of HCV genotype 2 infection: Results of the real-world, clinical practice HCV-TARGET study. *Gut.* 2017;**66**(10):1844-52. doi: [10.1136/gutjnl-2016-311609](https://doi.org/10.1136/gutjnl-2016-311609). [PubMed: [27418632](https://pubmed.ncbi.nlm.nih.gov/27418632/)]. [PubMed Central: [PMC5595101](https://pubmed.ncbi.nlm.nih.gov/PMC5595101/)].
28. Cho Y, Cho EJ, Lee JH, Yu SJ, Yoon JH, Kim YJ. Sofosbuvir-based therapy for patients with chronic hepatitis C: Early experience of its efficacy and safety in Korea. *Clin Mol Hepatol.* 2015;**21**(4):358-64. doi: [10.3350/cmh.2015.21.4.358](https://doi.org/10.3350/cmh.2015.21.4.358). [PubMed: [26770924](https://pubmed.ncbi.nlm.nih.gov/26770924/)]. [PubMed Central: [PMC4712163](https://pubmed.ncbi.nlm.nih.gov/PMC4712163/)].
29. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Effectiveness of sofosbuvir-based regimens in genotype 1 and 2 hepatitis C virus infection in 4026 U.S. veterans. *Aliment Pharmacol Ther.* 2015;**42**(5):559-73. doi: [10.1111/apt.13300](https://doi.org/10.1111/apt.13300). [PubMed: [26113432](https://pubmed.ncbi.nlm.nih.gov/26113432/)].
30. Tacke F, Gunther R, Buggisch P, Klinker H, Schober A, John C, et al. Treatment of HCV genotype 2 with sofosbuvir and ribavirin results in lower sustained virological response rates in real life than expected from clinical trials. *Liver Int.* 2017;**37**(2):205-11. doi: [10.1111/liv.13206](https://doi.org/10.1111/liv.13206). [PubMed: [27428297](https://pubmed.ncbi.nlm.nih.gov/27428297/)].
31. Weiss JJ, Bhatti L, Dieterich DT, Edlin BR, Fishbein DA, Goetz MB, et al. Hepatitis C patients' self-reported adherence to treatment with pegylated interferon and ribavirin. *Aliment Pharmacol Ther.* 2008;**28**(3):289-93. [PubMed: [19086329](https://pubmed.ncbi.nlm.nih.gov/19086329/)]. [PubMed Central: [PMC2891196](https://pubmed.ncbi.nlm.nih.gov/PMC2891196/)].
32. Alavian SM, Hajarizadeh B, Bagheri Lankarani K, Sharafi H, Ebrahimi Daryani N, Merat S, et al. Recommendations for the clinical management of hepatitis c in Iran: A consensus-based national guideline. *Hepat Mon.* 2016;**16**(8). e40959. doi: [10.5812/hepatmon.guideline](https://doi.org/10.5812/hepatmon.guideline). [PubMed: [27799966](https://pubmed.ncbi.nlm.nih.gov/27799966/)]. [PubMed Central: [PMC5075356](https://pubmed.ncbi.nlm.nih.gov/PMC5075356/)].
33. Hesamizadeh K, Sharafi H, Rezaee-Zavareh MS, Behnava B, Alavian SM. Next steps toward eradication of hepatitis C in the era of direct acting antivirals. *Hepat Mon.* 2016;**16**(4). e37089. doi: [10.5812/hepatmon.37089](https://doi.org/10.5812/hepatmon.37089). [PubMed: [27275164](https://pubmed.ncbi.nlm.nih.gov/27275164/)]. [PubMed Central: [PMC4893415](https://pubmed.ncbi.nlm.nih.gov/PMC4893415/)].
34. Rezaee-Zavareh MS, Hesamizadeh K, Behnava B, Alavian SM, Gholami-Fesharaki M, Sharafi H. Combination of ledipasvir and sofosbuvir for treatment of hepatitis C virus genotype 1 infection: Systematic review and meta-analysis. *Ann Hepatol.* 2017;**16**(2):188-97. doi: [10.5604/16652681.1231562](https://doi.org/10.5604/16652681.1231562). [PubMed: [28233739](https://pubmed.ncbi.nlm.nih.gov/28233739/)].
35. Merat S, Sharifi AH, Haj-Sheykholeslami A, Poustchi H, Fattahi B, Nateghi-Baygi A, et al. The Efficacy of 12 weeks of sofosbuvir, daclatasvir, and ribavirin in treating hepatitis C patients with cirrhosis, genotypes 1 and 3. *Hepat Mon.* 2016;**17**(1). doi: [10.5812/hepatmon.44564](https://doi.org/10.5812/hepatmon.44564).

Table 1. Risk of Bias Assessment for the Included Clinical Trial Studies

First Author (Reference)	Random Sequence Generation (selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participant and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition)	Selective Reporting (reporting Bias)	Co-interventions to Treat Analysis	Intention to Treat Analysis	Group Similarity at Baseline	Compliance	Timing of outcome assessments	Other Biases	Score	Conclusion
Foster, G. R. (18)	-	-	+	+	-	-	-	-	-	-	-	-	10	Low
Zeuzem, S. (19)	?	-	+	+	-	-	-	-	-	-	-	-	9	Low
Lawitz, E. (20)	?	+	+	+	-	-	-	-	-	-	-	-	8	Low
Gane, J. E. (21)	?	-	+	+	-	-	-	-	-	-	-	-	9	Low
Jacobson, I. M. (12)	?	?	-	?	-	-	-	-	-	-	-	-	9	Low
Lawitz, E. (22)	+	+	+	+	-	-	-	-	-	-	-	-	8	Low
Omata, M. (14)	+	+	+	+	-	-	-	-	-	-	-	-	8	Low
Ahm, S. H. (23)	+	+	+	+	-	-	-	-	-	-	-	-	8	Low
Kao, J.H. (13)	+	+	+	+	-	-	-	-	-	-	-	-	8	Low