



# Efficacy and safety of sofosbuvir-containing regimens in patients with chronic hepatitis C virus infection after liver transplantation: a meta-analysis

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**Background:** This meta-analysis evaluated the efficacy and safety of a sofosbuvir (SOF)-containing regimen in patients with hepatitis C virus (HCV) infection after liver transplantation (LT).

**Methods:** We performed a systematic search for relevant published data on the PubMed, EMBASE, and Cochrane Library databases. Studies that evaluated any regimen in which SOF was used to treat patients with HCV infection after LT and reported the sustained virologic response 12 weeks (SVR12) after therapy were included.

**Results:** A total of 12 studies, involving 892 patients, were included in this analysis. The pooled estimate of SVR12 (sustained virologic response 12 weeks) was 88.1%. Subgroup analysis showed that patients who received SOF plus other DAAs had higher SVR12 than those treated with SOF plus ribavirin or peg-IFN. The pooled incidence of any adverse events (AEs) was 73.7%.

**Conclusions:** The results of this study showed that the treatment response of SOF-containing regimens in patients with HCV infection after LT was satisfactory. However, more attention needs to be paid to the high rate of AEs associated with such regimens.

**Keywords:** Sofosbuvir; hepatitis C virus infection (HCV infection); liver transplantation (LT); sustained virologic response 12 weeks (SVR12); meta-analysis

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## Introduction

Hepatitis C virus (HCV) infection is the leading indication for liver transplantation (LT) worldwide (1,2). In patients with whom the virus is detectable at the time of transplantation, the recurrence of HCV is universal and immediate (3,4). Aggressive clinical features often characterize recurrent HCV infection after LT, and patients can rapidly progress to cirrhosis, decompensation, and increased risk of morbidity and mortality (5-7). For patients

with recurrent HCV infection after LT, the treatment options are complicated (8). Those treated with pegylated interferon (Peg-IFN) and ribavirin often experience low rates of sustained virologic response (SVR) and significant adverse effects (9). While triple treatments with protease inhibitors have slightly improved the efficacy, they exacerbate adverse events (AEs) (10). Therefore there is a great need for a regimen that is both more potent and more tolerable without drug interactions for LT patients with

recurrent HCV infection (8).

The development of direct-acting antivirals (DAAs) for the treatment of HCV has been eagerly anticipated. SOF, an oral nucleotide analog inhibitor of the HCV non-structural 5B (NS5B) polymerase, has recently been approved for the treatment of HCV genotypes 1–4. As reported, SOF, in combination with other DAAs or ribavirin, has demonstrated excellent efficacy and low rates of AEs (11,12). To date, no study has carried out a comprehensive evaluation of the efficacy and safety of SOF-containing treatment for patients with recurrent HCV infection after LT. This study aims to summarize the currently available data on the treatment of recurrent HCV in patients after LT with SOF and to supply guidance in practical clinical algorithms.

We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-3074>).

## Methods

### *Searching strategy and literature selection*

The literature search and data collection were performed in January, 2018. Three electronic databases, including the PubMed, EMBASE, and Cochrane Library databases, were searched. The literature search was performed using the following terms: “hepatitis C” or “HCV” or “hepacivir\*”; “sofosbuvir” or “Sovaldi” or “SOF” or “GS-7977” or “PSI-7977”; “liver transplantation.” A manual search for potentially eligible studies was also performed by checking the references of the included studies and published narrative reviews.

We collected clinical trials, prospective cohort studies, or case-control studies that assessed the efficacy and safety of the SOF-containing regimens in patients with recurrent HCV infection after LT. Studies meeting the following criteria were included: (I) the study population were patients with recurrent HCV infection after LT; (II) the therapy included SOF; (III) the primary outcome was SVR12 (sustained virologic response 12 weeks) and the data of SVR12 was available; and (IV) the study showed safety-related outcomes. Studies were excluded if they met any of the following criteria: (I) the participants did not undergo LT; (II) the primary outcome measure was not SVR12, or the value of SVR was not available; or (III) conference abstracts without full text.

All the reviewing and screening processes in this study

were based on the PRISMA guidelines for reporting systematic reviews. At each stage of the screening, we discussed the included and excluded studies, and resolved any discrepancies.

### *Data extraction*

The following data were extracted from each study: first author’s name, publication time, study design (including sample size, drug dose, and treatment duration), patients’ clinical characteristics (including age, sex, HCV RNA level, and indications of liver function), and efficacy and safety outcomes.

The methodological quality of each study included in this analysis was assessed by the Jadad Scale (13), which has three items: randomization, blinding, and withdrawals and dropouts. The lowest score is 0, and the highest score is 2 for the first 2 items and 1 for the third item. The total score for each study can range from 0 to 5. The studies that scored 3 or more were considered to be of a higher quality.

### *Statistical analysis*

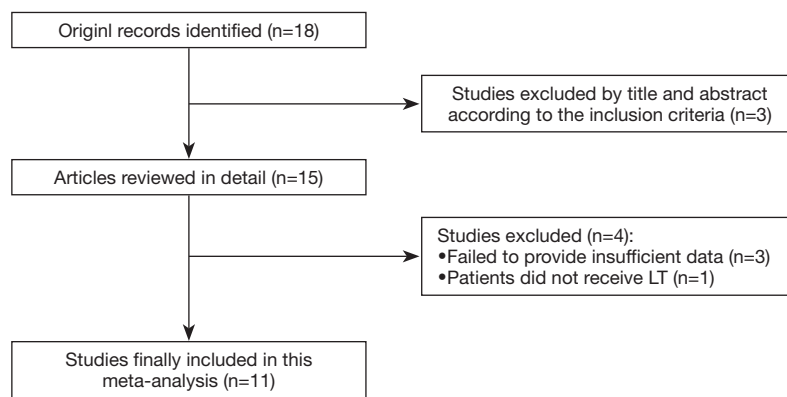
All the analyses were performed using Stata (version 13.0). The statistically significant level was set at 0.05. Heterogeneity test was performed using  $\chi^2$  and  $I^2$  indices. If heterogeneity existed among the included studies, then a random effects model was used. Otherwise, a fixed effects model was adopted (14). Publication bias was assessed by Begg’s test, along with a funnel plot (15). Meta-regression analysis was also performed.

## Results

### *Characteristics of the included studies*

A total of 18 potentially relevant studies were found through the electronic searches. After a review of titles and abstracts, 15 articles were chosen for a full review. Finally, 11 articles (involving 12 studies) meeting the inclusion, and exclusion criteria were included in this meta-analysis (8,11,16–24). The selection process is shown in *Figure 1*.

The selected papers involved 892 patients with recurrent HCV infection after LT who were treated with a SOF-containing regimen. The percentage of men in each study ranged from 33.3–87.5%. The median age of the patients ranged from 51–60 years. The baseline characteristics of the patients are shown in *Tables 1* and *2*.



**Figure 1** Flow diagram of study selection process.

**Table 1** Baseline characteristics of participants<sup>†</sup>

First author	Year	Study design	Combination drugs	Sample size (person)	Age (years)	Male (%)	Time after LT (years)
Charlton	2014	Multicenter, open label	Ribavirin	40	59 [49–75]	31 (77.5)	4.3 (1.0–10.6)
Pellicelli	2014	Multicenter, single arm	Daclatasvir+/Ribavirin	12	58 [7]	7 (58.3)	1.6 (1.4)
Punzalan	2015	Prospective study	Simeprevir	42	58	14 (43.75)	2.3
Leroy	2015	Prospective study	Daclatasvir/Ribavirin	8	54	7 (87.5)	0.9 (0.4–2.05)
Leroy	2015	Prospective study	Daclatasvir/Ribavirin	15	51	12 (80.0)	0.4 (0.3–1.5)
Forns	2014	Single arm	Ribavirin+/IFN	92	55 [51–60]	76 (82.6)	1.5 (1.4–4.5)
Charlton	2015	Phase 2, open label	Ledipasvir + Ribavirin	229		192 (83.8)	4.48
Levitsky	2016	Open label phase 2 study	Ledipasvir	16	59 [52–72]	8 (50.0)	NA
Ajlan	2016	Open label prospective cohort study	Ribavirin+/peg-IFN	34	56.3 [27–30]	24 (70.6)	5.5
Dumortier	2016	Prospective, multicenter	Daclatasvir/Ribavirin/ Ledipasvir/smv	125	59.4 [9.0]	98 (78.4)	7.9
Manns	2016	Multicenter, open-label study	Ledipasvir + Ribavirin	226	NA	174 (77.0)	4.5
Poordad	2016	Open-label study	Daclatasvir	53	NA	NA	NA

<sup>†</sup>, data are displayed as median (range) or mean (SD) or n (%). LT, liver transplantation; Peg-IFN, pegylated interferon.

### Efficacy outcome

The pooled analysis of SVR12 is shown in *Figure 2A*. A random effects model was adopted because the I<sup>2</sup> was over 80% ( $\chi^2=62.21$ ,  $P<0.01$ ). Two studies were excluded, as all participants achieved SVR12. The pooled SVR12 was 88.1% (95% CI: 82.8–93.3%).

### Safety outcomes

By pooling the data from 7 of the 12 studies, we found that

the heterogeneity of incidence of discontinuation existed ( $\chi^2=29.54$ ,  $P<0.01$ ). The pooled estimate of the rate of discontinuation was 6.5% (95% CI: 2.4–10.7%) (*Figure 2B*). The heterogeneity of the incidence of AEs and serious adverse events (SAEs) also had statistical significance ( $\chi^2=239.02$ ,  $P<0.01$ ;  $\chi^2=63.89$ ,  $P<0.01$ ). The pooled estimates of the rate of AEs and SAEs were 73.7% (95% CI: 62.7–84.6%) and 22.1% (95% CI: 14.4–29.7%), respectively (*Figure 2C,D*).

The most common AEs were anemia, nausea, renal

**Table 2** Clinical characteristics of participants<sup>†</sup>

First author	HCV RNA (log IU/mL)	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	GGT (IU/L)
Charlton	6.74 (4.49–7.59)	68 [16–391]	79 [30–319]	NA	NA
Pellicelli	5.95 (1.3)	97 [34–376]	NA	NA	NA
Punzalan	NA	NA	NA	NA	NA
Leroy	6.9	132 [101–172]	209 [145–371]	210 [181–648]	287 [152–500]
Leroy	6.9 (6.3–7.6)	131 [49–188]	226 [83–306]	415 [184–528]	816 [499–1,603]
Forns	6.2 (5.3–7.0)	71 (39.3–167.0)	124.5 (70.8–210.5)	164.0 (117.5–263.3)	144.0 (64.0–426.5)
Charlton	6.46	NA	NA	NA	NA
Levitsky	5.8 (4.1–6.7)	50 [11–150]	99 [33–203]	NA	NA
Ajlan	6.9 (7.3)	69.7 (59.2)	67.3 (47.2)	181.2 (139.4)	422.2 [612]
Dumortier	6.1 (1.0)	91.6 (70.9)	81.2 (53.4)	153.0 (103.3)	278.3 (295.1)
Manns	6.4 (0.5)	NA	NA	NA	NA
Poordad	NA	NA	NA	NA	NA

<sup>†</sup>, data are displayed as median (range) or mean (SD). ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, glutamic pyruvic aminotransferase; GGT, glutamate transpeptidase; HCV, hepatitis C virus; RNA, ribonucleic acid.

failure, aminotransferase increase, fatigue, and joint pain. Pooled results from 6 of the 7 studies revealed high heterogeneity.

### Subgroup analysis and Meta-regression analysis

Subgroup analysis showed that patients treated with SOF plus other DAAs had higher SVR12 than those treated with SOF plus ribavirin or peg-IFN ( $\chi^2=43.35$ ,  $P<0.01$ ; *Figure 3*).

We performed a meta-regression analysis to explore the factors associated with the effect and safety outcomes. The data that was taken into consideration were: age, the proportion of men, time from liver transplantation (LT), the level of HCV RNA, alanine aminotransferase (ALT), alkaline phosphatase (ALP), glutamic pyruvic aminotransferase (AST), and glutamate transpeptidase (GGT). The result showed that the levels of ALT and AST were associated with the rate of SAEs ( $t=3.44$ ,  $P=0.01$ ;  $t=2.95$ ,  $P=0.032$ ).

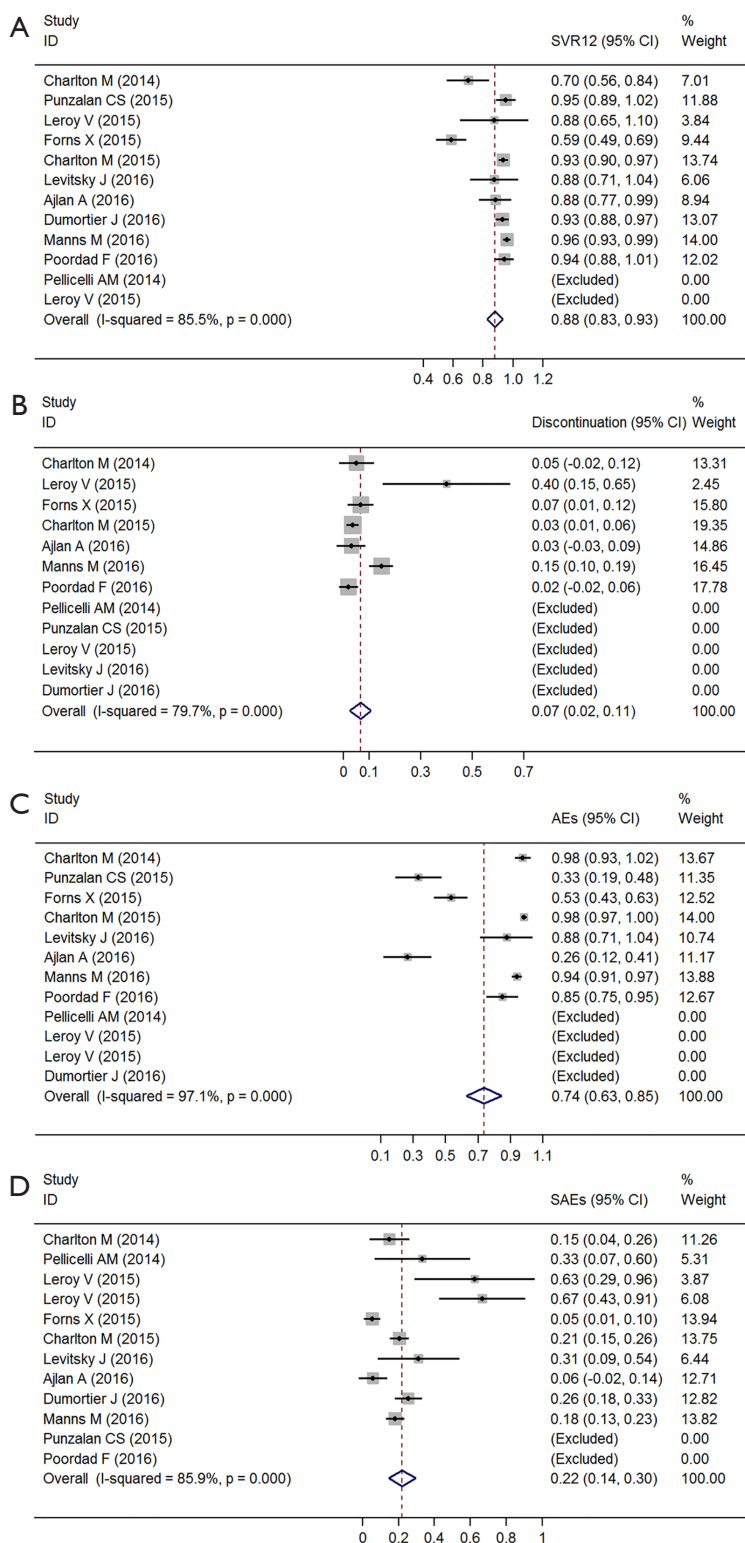
### Publication bias

Begg's test was performed to evaluate publication bias and revealed no statistical significance ( $z=1.43$ ,  $P=0.15$ ). The funnel plot for SVR12 is shown in *Figure 4*. The studies were distributed closely within the 95% confidence interval axis, which indicated no obvious publication bias.

## Discussion

This meta-analysis evaluated the efficacy and safety of SOF for the treatment of patients with recurrent HCV infection after LT and found that the SVR12 was 88.1% (95% CI: 82.8–93.3%) and the rate of any AE was 73.7% (95% CI: 62.7–84.6%).

SOF is a potent NS5B nucleotide polymerase inhibitor with all HCV genotype activity and a high barrier of resistance (25). While it is currently an attractive target for anti-HCV treatment, the effect in patients who have received LT is still unclear. This study was the first study that aimed to evaluate a drug in post-transplant patients with recurrent HCV infection. Our findings show a potent efficacy and a favorable safety profile for SOF-containing regimens. Based on regression analysis, the efficacy of the regimens was not associated with valuable clinical indexes. Subgroup analysis of patients who received combination therapy found that treatment with SOF and other DAAs showed higher SVR12 than those treated with SOF and RBV or peg-IFN. Previous studies have shown that RBV is not needed when SOF and daclatasvir are used (16,26). Despite the increased rate of side effects and decreased effect with RBV, the possibility of shorter treatment time and reduced cost may lend support to the use of RBV, especially in patients for whom prior treatment has failed (27). However, a more extensive study is needed to confirm



**Figure 2** Forest plot of efficacy and safety outcomes. (A) Forest plot of SVR12; (B) forest plot of discontinuation; (C) forest plot of serious adverse events; (D) forest plot of any adverse events.

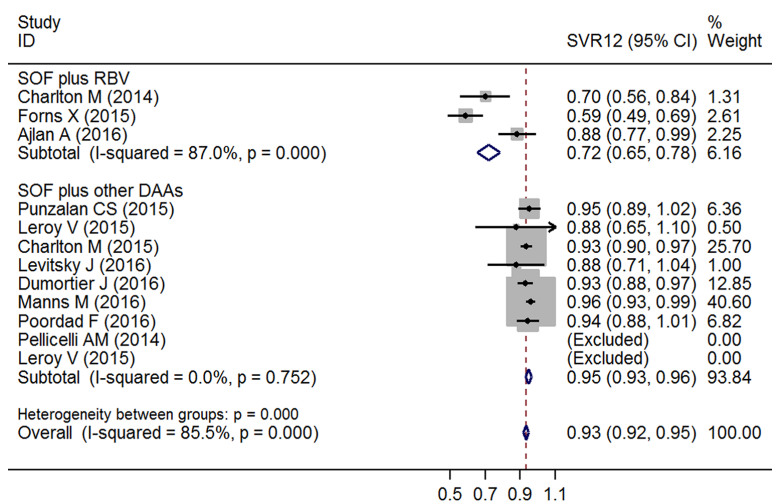


Figure 3 Forest plot of SVR12 based on treatment therapy.

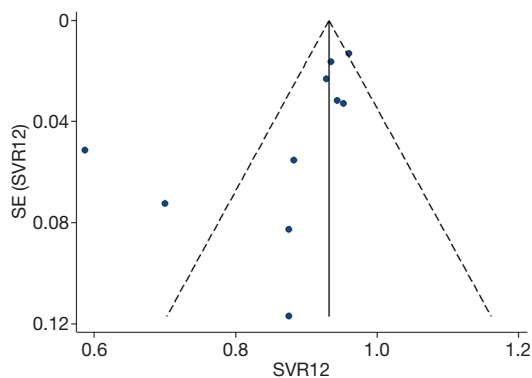


Figure 4 Funnel plot for SVR12 with pseudo 95% confidence limits.

that RBV does not increase the efficacy in patients with recurrent HCV infection after LT.

Our study also showed a high SAE rate in this patient population. We performed regression analysis and found that the levels of ALT and AST were associated with the rate of SAEs, which indicates that the high SAEs were not related to the study drugs but rather to the underlying liver disease. These findings strongly suggest that post-LT patients should receive treatment early on and that use in advanced liver disease should be discouraged (17). Although the heterogeneity was significant, it can be accounted for by the different combination therapies used in subgroup analysis.

There are some limitations in this meta-analysis that should be considered. First, since our study only focused on

post-transplant patients with HCV infection patients, we could not assess the efficacy and safety of SOF-containing regimens in patients with other advanced liver diseases. Second, single-arm trials were included; thus, we could not derive the absolute values of safety and efficacy indexes, and the present information was not sufficient to allow a precise subgroup analysis based on HCV genotype, level of disease, or treatment duration. Third, we did not conduct a cost-effective analysis to assess the benefit of the treatment regimen. Finally, as the number of included studies was small, more large-scale, and longer-term studies based on survival outcomes and the increasing safety profiles evaluating SOF-containing regimens will be of interest.

### Conclusions

In summary, the present meta-analysis suggests that SOF-containing regimens have proved useful for the treatment of patients with recurrent HCV after LT. Compared to RBV or peg-IFN, patients treated with SOF combined with other DAAs have higher SVR12. In post-LT patients, treatment should be started early, and use in advanced liver disease should be taken into consideration. Further studies to investigate survival and safety outcomes for patients are needed.

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## Footnote

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-3074>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-3074>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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